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**The Splendid Coöperation with the Bodies That Had Their Inception within the American Pharmaceutical Association and Continue to Hold Their Meetings with the Parent Organization Speaks for Their Common Interests.**

Vol. XXII, No. 7 JULY, 1933

# JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

TRADE MARK

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THE 81st ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION WILL BE HELD IN MADISON, WISCONSIN, AUGUST 28 TO SEPTEMBER 2, 1933, HOTEL LORAINE, HEADQUARTERS, EMERSON STANLEY, 602 CENTRAL BUILDING, MADISON, LOCAL SECRETARY.

The 1933 Meetings of the American Association of Colleges of Pharmacy, the National Association of Boards of Pharmacy, Conference of Pharmaceutical Association Secretaries, of the Pharmaceutical Law Enforcement Officials and the Plant Science Seminar will also be held in Madison.

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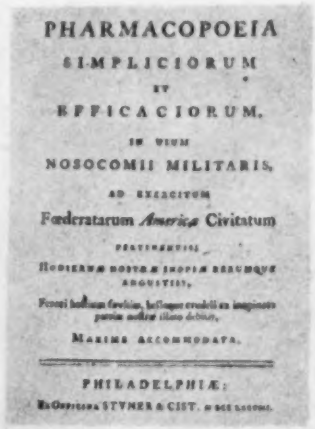
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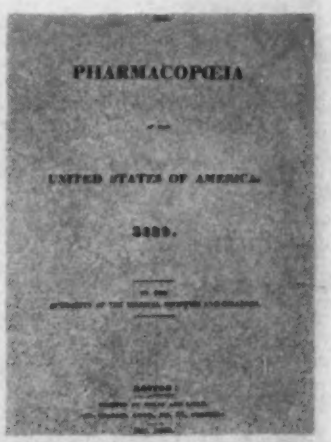
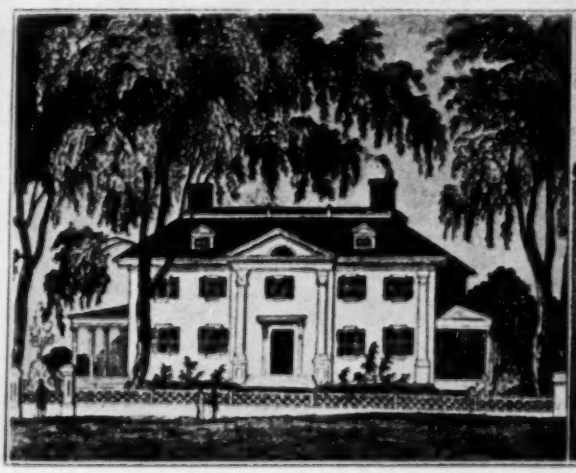
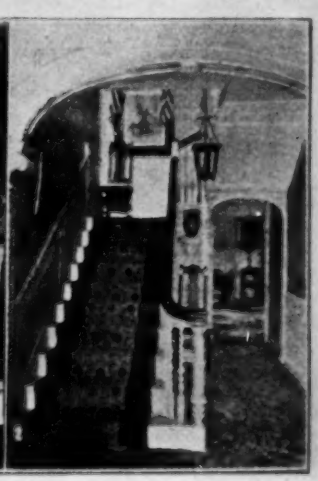
Reduced title page, American Military Pharmacopœia (1778). Reading text 2½ x 4½ inches. (Dr. William Brown.)


PHARMACOPŒIA
UNITED STATES OF AMERICA.
1820.

Reduced title page U. S. Pharmacopœia I (1820). Reading text 3½ x 6 inches. (Dr. Lyman Spalding.)

Above, Christopher Marshall; below, Dr. John Morgan. In the group of three: left, General (Dr.) Hugh Mercer; center, Dr. Lyman Spalding; right, Dr. William Brown. In the illustration below—Washington's Headquarters at Cambridge; herein Apothecary-General Andrew Craigie had his office. On the right is shown the East Entry to the Medical Headquarters.





General view of the pharmaceutical exhibit as a whole. Note the difficulties encountered on account of the pillars.

Detailed view of the west wall; the platform at the left is part of the Historical Rotunda.

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

VOL. XXII JULY, 1933 No. 7

## THE PHARMACY EXHIBIT—A CENTURY OF PROGRESS INTERNATIONAL EXPOSITION.

PHARMACISTS will have pride in the pharmacy exhibit at the World's Fair, in Chicago, and be greatly pleased with the impression made on the visitors. The exhibit reflects credit on pharmacy and brings its message to the public in a way never before possible, and the displays of other branches of the medical sciences and public health activities, together with those of the divisions of related industries, complement and supplement each other in a most interesting and informative portrayal of pharmacy and its service.

Chairman H. C. Christensen and Secretary Frank B. Kirby have made it possible for the writer to acquaint the readers with the exhibit by illustrations and descriptions. The pillars make it difficult, if not impossible, to present complete details in one picture, hence several views are shown, and the explanatory descriptions supplied by Chairman Christensen enable the writer to describe the exhibits in more or less detail. The photographs were made by Kaufmann-Fabry—the official photographer—mention here serves the purpose of the usual courtesy line under each photograph.

A glass case on the central dais contains a reproduction from the "Ebers Papyrus." The display recesses at both ends of the picture are only partially visible on account of the obstruction by the pillars. Left to right, in Recess No. 1, a double space, the story of Cinchona is depicted—there are four colored drawings of the plant but only part of one drawing is visible in the photograph; the drawings form the background of the display, showing branches, leaves and seed pods. Several jars and one large package of cinchona bark are included in the display; two of these were exhibited at the 1893 Fair in Chicago. At the left, not visible in the picture, is an illuminated map showing the countries in which cinchona is native, where it is cultivated and where malaria was very prevalent. Cards call attention to the medicinal use of the bark and its preparations, the alkaloidal discoveries and the value of this important drug to the world.

Detailed view of the Historical Rotunda. The inscription above is from Ecclesiasticus 38: 4, 6.

Detailed view of the first drug store in Chicago (Philo Carpenter). A modern pharmaceutical and chemical laboratory. Digitalis display.

A complete line of U. S. P. and N. F. preparations is shown in Recess No. 2 and attention is called to progressive improvements in their manufacture and standardization, resulting in more elegant and efficient preparations. The art and science of pharmacy are contrasted and importance of accuracy and uniformity stressed.

The compounds and preparations of iodine are featured in Recess No. 3. The next display (double space) shows preparations compounded in accordance with the first pharmacopœia published in the United States, that of the military hospital established by General George Washington at Lititz, Pa., and compiled by Dr. William Brown (see JOURNAL A. PH. A., October 1930, page 1041). This represents the first attempt in the United States to establish uniformity in pharmaceutical preparations and in that sense may be termed the forerunner—of the U. S. Pharmacopœia, established by Lyman Spalding—of the National Formulary, and of the "Recipe Book." The value of standardization is brought to the attention of the visitors.

The next displays show the evolution of pharmaceutical journals and of pharmaceutical textbooks. Recess No. 7, another double section, is devoted to the AMERICAN PHARMACEUTICAL ASSOCIATION; above is a photo mural depicting the American Institute of Pharmacy and the "ground-breaking ceremony;" in the center is a mural of the building in Philadelphia where, in 1852, the ASSOCIATION was organized. Bound and unbound JOURNALS, PROCEEDINGS and YEAR BOOKS are shown.

Photograph No. 4 shows a reproduction of Chicago's first drug store, that of Philo Carpenter, one of the city's outstanding citizens of that period. Items of historical and pharmaceutical significance are included in this division; also a modern pharmaceutical and chemical laboratory where, daily, instructors and students and graduates of nearby colleges of pharmacy give demonstrations. At the right is a "digitalis display," telling the story of this important drug, from farm to pharmacy; oil paintings, photographs and cards tell its story and that of Old Lady Shropshire and Dr. Withering.

Group 5 includes the educational and public health displays. The revolving globes with maps give statistics on the number of colleges of pharmacy and the number of drug stores, and in the photo mural background the educational institutions of the earlier and present period are contrasted. The materia medica display gives to the public information anent the development of drugs employed in medicine—of the changes and progress during the century. This section also tells the story of legislation and related statistics. Chairman Christensen and Miss Barney are shown in the picture.—See end of last page of "Bibliography of Pharmaceutical Research."

It is hoped, later, to present other views in which details will be brought out that were not caught by the camera in these photographs.

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## FERRETS SUSCEPTIBLE TO INFLUENZA.

The *Lancet* reports the discovery by Drs. Wilson Smith, C. H. Andrewes and P. P. Laidlaw, of the National Institute for Medical Research, that ferrets are susceptible to influenza. Heretofore it had been impossible to infect animals, and the successful discovery, it is hoped, will result in finding a vaccine to combat the disease.

# EDITORIAL

E. G. EBERLE, EDITOR 10 West Chase Street, BALTIMORE, MD.

## RATIFICATION OF THE NARCOTICS LIMITATION CONVENTION.

THE promulgation of League of Nations Narcotic Treaty became effective on July 10th and its importance was announced to the public in a radio program on July 9th, in which speakers of national prominence, including President Roosevelt, participated. The action by manufacturing and other nations is confidently expected to constitute an effective and important step in the direction of suppressing the evils of the illicit narcotic traffic and of reducing the production of narcotics to the amounts needed for medical and scientific purposes.

While "listening in," the radio program suggested this as a timely opportunity to speak briefly of pharmacy's contributions to the suppression of narcotic addiction. Long before legislation was enacted for regulating the dispensing of narcotics and preparations containing them, pharmacists studied ways and means for checking the increase of narcotic medication and resulting addiction. No group has more persistently and consistently advocated regulations for controlling the sale of narcotics to safeguard public health than have pharmacists, and officials have stated on a number of occasions that pharmacists have given the best of coöperation. It seems almost unbelievable, but nevertheless a fact, that when pharmacists first made concerted efforts to have restrictive legislation enacted, they found objection by legislators who thought there must be an ulterior motive back of their efforts, because it reduced sales volume.

Coming nearer to the time of enactment of the Harrison antinarcotic law the PROCEEDINGS of the AMERICAN PHARMACEUTICAL ASSOCIATION contain reports and papers on the subject and reference to some of them will be pardoned. On page 567 of Volume 50 of the PROCEEDINGS is the report of Chairman H. P. Hynson which gave impetus to continue the study of addiction by the ASSOCIATION. In Volume 51 is another report of the Committee (page 466) and a paper by James H. Beal—"An Antinarcotic Law," which may be designated as a step toward national legislation relative to the handling of narcotics, for at the same meeting a draft for an antinarcotic law was submitted and a revision of it at the 1904 meeting (page 104) at which time also a paper on "Pharmaceutical Legislation with Special Reference to Antinarcotic Laws" (page 180) was presented. The report made at the 1905 meeting indicates how seriously the conditions were viewed by pharmacists throughout the country. That Congress did not realize the importance of antinarcotic legislation is evidenced by the fact that the federal law was not enacted until December 1914. The law added burdens to the many willingly assumed by pharmacists, quoting the closing paragraph of an editorial (1913) in advocating the passage of a federal antinarcotic law: "It must not be imagined that any form of law can be devised that will be entirely free from objections, or that will not impose some burdens upon pharmacists and physicians, no matter how conscientious they may be in the handling of these drugs.

"Since society began those who have been willing to deal justly with their fellow men have been compelled to bear the burden of laws intended to curb the actions of those who are not controlled by conscientious motives, and no one has yet

been able to suggest a method that will relieve the honest and conscientious citizen from this hardship."

The references made are not intended to take credit for performing a duty to mankind, but to call attention to the important services rendered by pharmacists, because they recognized their duty long before general recognition was given to the control of narcotic sales and all divisions of pharmacy entered into this service. It is contended in the interest of the public, that the sale and dispensing of all medicines be restricted to those who because of training and education know the effect of medicines and realize their individual responsibility, as professional men and women, in safeguarding the public.

The Association sponsoring the radio program spoke for uniform state anti-narcotic laws. The subject has recently (October 1932, page 989) received editorial consideration and need not be further discussed at this time. Pharmacists are awake to their responsibilities, they understand the needs and are appreciative of the support of all good citizens; "they desire to assist in strengthening the federal and state laws and in making them uniform, in so far as this is possible, and will assist heartily in adequate control."

The ratification of the Narcotics Limitation Convention is an important step in suppressing the evils of illicit narcotic traffic, which has been the great source of trouble; the legalized sale may be further controlled, but at the present reflects credit upon pharmacy in its several divisions and the prescribers of medicine.

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## PROGRESSIVE THOUGHTS ON COÖPERATION.

NEVER before has there been greater need of general coöperation of pharmaceutical organizations than at present. Just as state associations depend on the loyalty and support of individual membership, so also the body pharmaceutic must realize that progress is stimulated by a sense of loyalty and faith in the profession of pharmacy. The House of Delegates of the AMERICAN PHARMACEUTICAL ASSOCIATION is the forum for discussing problems of pharmacy where the associations may gain strength and understanding for meeting the situations that await improvement for their own good and of the public served by them.

At the Diamond Anniversary Meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION in St. Louis, Surgeon McLaughlin, representative of the U. S. Public Health Service, said that he expected to find his greatest interest in the Scientific Section and he profited by the papers read there, but his interest was amazingly increased by attending other ASSOCIATION divisions which gave him an idea of the scope of the AMERICAN PHARMACEUTICAL ASSOCIATION, and the thing that challenged his admiration more than anything else was the evident broadening scope from a purely scientific organization, the broad statesmanship displayed in the laudable effort to bring together many divergent interests which have, however, one objective in common—the advancement of pharmacy. He considered that a most hopeful augury for the future of pharmacy in the United States and emphasized the ASSOCIATION'S opportunities and the possibilities and usefulness of bringing together the divergent interests of the drug interests and of pharmacy for exchange of ideas and working out problems of mutual benefit.

The splendid coöperation with the bodies, state associations and others, that had their inception within the AMERICAN PHARMACEUTICAL ASSOCIATION have to-day a growing opportunity to bring about a better service and this is made possible by the House of Delegates, the Conference of Pharmaceutical Association Secretaries, the Law Enforcement Officials and other bodies meeting concurrently and now preparing programs for the meeting to be held in Madison. These are times when as never before wise conferences and discussions will be helpful and profitable.

The last meeting held in Wisconsin by the AMERICAN PHARMACEUTICAL ASSOCIATION (1884) was presided over by the late William S. Thompson. Liberty is taken in quoting from his presidential address which may be applicable to-day: "During the past year, pharmacists of this country have been greatly concerned in an effort to secure remunerative retail prices for what are known as proprietary medicines. The prominence which the agitation of this question has assumed, combined with its possible influence on pharmacy as a profession, renders some reference to the topic almost indispensable at this annual assemblage, not for the purpose of discussing the proposed methods for accomplishing fair prices in the sale of these articles, for that properly belongs to a kindred organization, but of considering the effect of this agitation on the future of pharmacy."

In another part of his address he asks "Are we not justified in the belief that from the present trade conflict there will survive a higher pharmacy than that of our time? We are sustained in this opinion by a survey of the entire situation of pharmacy in this country." "...characteristic of our country in all that pertains to science and art—our profession will not lag behind, but the followers fully equipped with knowledge and skill, will stand shoulder to shoulder with the most advanced; and with equal strides will move on to that brighter era for which they appear to be preparing."

Times have changed, but in part what President Thompson said may be applied to the present conditions. What was stressed at the St. Louis meeting finds application now and our duty is to study the conditions which affect us and bettering them for greater service. The surveys that have been made of pharmaceutical practice are being studied and reported for the benefit of all concerned and, as never before, the standards soon to become official will serve the public in a larger way—unfolding opportunities that will be greatly strengthened with the completion of the Pharmacy Building in Washington.

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## ATTENDANCE AT CHICAGO WORLD'S FAIR.

Attendance for the first month, May 27th to June 27th, at the Chicago World's Fair—A Century of Progress—was 2,464,413. For two weeks after the opening the attendance averaged 60,000 a day. The third week the average jumped to 81,000 a day and the fourth week it went to 112,251 a day. In its first month the Chicago World's Fair of 1893 had 1,050,000 paid admissions.

The biggest day in the first month of A Century of Progress was June 23rd, Finnish Day of Scandinavian week, with 139,452. Next was June 18th, featured by the Kiwanis International assembly, with 132,490. Visitors' registration book in the Sears Roebuck Building near the North Entrance on June 25th had more than 150,000 entries including visitors from sixty-four different foreign countries and registrations from every state in the United States and every province in Canada.

The attendance at the Pharmacy Exhibit is very gratifying, not only in the number of visitors, but more particularly because of the interest shown by them in studying the displays.

# SCIENTIFIC SECTION

BOARD OF REVIEW ON PAPERS.—*Chairman*, L. W. Rowe; John C. Krantz, Jr.; F. J. Bacon.

## STUDIES ON THE BIOASSAY OF DIGITALIS: FROG METHODS.

BY JAMES H. DEFANDORF.

### INTRODUCTION.

Although the frog heart-lymph sac method for the bioassay of digitalis has been official in the United States for almost a decade and a half, it has been the object of considerable criticism (3, 6, 9, 22, 23, 24, 27, 29, 30), and as a result numerous other methods (5, 6, 7, 14, 20, 22, 25, 28, 30, 31, 32) have appeared since its adoption by the United States Pharmacopœia (33). It is probable that the chief reasons for its continued recognition in the pharmacopœia are its simplicity, economy, reasonable accuracy and because it is considered to be a relatively good index of therapeutic activity.

The method of the United States Pharmacopœia limits the observation period to one hour, requires an assay temperature of 20° C., and does not refer to the sex of the frogs, whereas the method of the Geneva Conference of the League of Nations (22) designates an observation period of at least four hours, places no limitations on the assay temperature and specifies male frogs.

With these differences in mind, the following studies dealing with the assay of digitalis on frogs were made:

1. Comparison of absorption in the one- and four-hour lymph sac methods.
2. Influence of temperature and of sex on absorption from the lymph sac.
3. Toxicity of digitalis by the one-hour and four-hour lymph sac, the intramuscular and the intravenous methods.

### LITERATURE.

Since the conflicting results of various workers may be due largely to lack of uniformity in the experimental conditions and technique, a review of the literature is given below in classified form which indicates some of the probable causes leading to variable results.

*1. Species.*—The U. S. P. X (33) specifies the use of the grass frog, *Rana pipiens*, while the variety known as *Rana temporaria* is generally employed in Europe. Either of these two varieties of grass frogs may be used in the method of assay described by the Geneva Conference of the League of Nations (22).[1]

*2. Health.*—No comment is necessary on the importance of this factor. Health can probably best be maintained by keeping the frogs in running water at a temperature not exceeding 15° C., as required in the U. S. P. X (33).

*3. Size.*—Houghton (16) stated that frogs of nearly uniform size should be used and based the dosage upon body weight, and later (17) recommended 15 Gm. as the standard. Famulener and Lyons (10) used 40 Gm. and Focke (11) 25- to 30-Gm. frogs, while Roth (26) and Smith and McClosky (27) worked with 20- to 30-

[1] Hereafter referred to as "Geneva Conference."

Gm. frogs, the limits specified by the U. S. P. X (33). The method of the Geneva Conference allows animals weighing up to 40 Gm. These marked variations are not surprising in view of the difficulty in procuring large numbers of frogs of uniform weight.

*4. Sex.*—Buhrer (4) assaying digitalis on *Rana temporaria* by the frog heart-lymph sac method, concluded that females were more uniform in response than males, and finally employed females exclusively. Focke (11) believed that sex was not a factor in July, August and September. Edmunds and Hale (8) found sex a factor only in the spring months, but later Hale (12) stated that even in the mating season the greater weight of females due to enlargement of the egg sac does not render them more susceptible to digitalis when the dose is estimated on body weight. This observation was corroborated by Sollmann, Mendenhall and Stingell (29) working with ouabain, who nevertheless rejected females during the breeding season. Baker (1) found sex relatively unimportant except when the female contained a very large egg mass, when it appeared slightly more resistant. Roth (26) working with digitalin, observed a more variable absorption with females, but found that the occurrence of eggs bore no relation to the degree of absorption. No mention of sex or the occurrence of egg-masses is to be found in the method of the U. S. P. X (33), but the method of the Geneva Conference (22) specifies the use of male frogs.

*5. Seasonal Influence.*—Seasonal variation is rather intimately bound up with sex and susceptibility. Houghton (16) and Edmunds and Hale (8), believed that frogs could be used throughout the year, if the conditions were identical and if comparisons were made with a standard. Edmunds and Hale (8), however, concluded that summer assays were best. Focke (11) found that susceptibility varied only slightly in July, August and September. Hale (12) concluded that tests of digitalis by the frog heart-lymph sac method did not vary 10 per cent from September to March. Baker (2) found poor absorption most likely to occur in the spring and late autumn. Smith and McClosky (27) observed that when frogs are kept at 20° C. there is little variation in seasonal susceptibility.

*6. Influence of Temperature.*—Houghton (16), Famulener and Lyons (10) and other early investigators did not specify definite temperature limits for their assays. Focke (11) and Edmunds and Hale (8) kept the frogs at a temperature of not over 17° C. Hale (12, 13) later designated 22° C. as the standard for his tests. Baker (1, 2) found a more ready absorption at higher temperatures, the minimum lethal dose varying inversely with the temperature. The results of Baker were confirmed by Sollmann, Mendenhall and Stingell (28, 29) while working with ouabain. They found in addition that the increase of toxicity per degree of temperature was much greater at lower than at higher temperatures between the ranges of 10° and 20° C., an observation that is in harmony with the law of the effect of temperature upon biological reactions. Roth (26) found a better absorption of digitalis preparations at 30° and 20° C. than at 10° C. Smith and McClosky (27) found that the sharpness of the end reaction was best at 20° C. The U. S. P. X (33) requires an assay temperature of 20° C. while the standard of the Geneva Conference (22) does not specify a standard temperature.

*7. Amount of Fluid Injected.*—Houghton (16, 17) using 15-Gm. frogs, injected 0.5 cc. of fluid into the ventral lymph sac, whereas Famulener and Lyons (10) used

the same amount for 40-Gm. frogs. Focke (11) injected 0.3 cc. into each of the two leg lymph sacs. Sollmann, Mendenhall and Stingell (29) specified not more than 1 cc. of fluid. Roth (26) found 0.5 cc. of fluid satisfactory for either leg or ventral lymph sacs. Hale (13) specified 0.015 cc. of fluid per Gm. for 20- to 35-Gm. frogs, as did Baker (1, 2) who stated that a majority of healthy frogs will in one hour absorb that quantity of fluid from the ventral lymph sac. The U. S. P. X (33) requires 0.015 cc. per Gm. for 20- to 30-Gm. frogs. The Geneva Conference (22) specified that not more than 0.3 cc., or with weakly active preparations, not more than 0.5 cc., of fluid should be injected into the ventral lymph sac, any excess being injected into one or both thigh lymph sacs.

*8. Character of Fluid Injected.*—The liquid preparations of digitalis are aqueous or hydro-alcoholic in character; hence dilutions of these liquids for injection into the lymph sac will contain varying proportions of alcohol and water or physiological saline. Houghton (16, 17) dissolved strophanthin in physiological saline. Famulener and Lyons (10) made all their dilutions with physiological saline, being careful to have the same alcoholic content in every case. Baker (2) found that physiological saline was more readily absorbed from the lymph sac than distilled water, 25% alcohol more readily absorbed than physiological saline, but that 50, 75 and 90% alcohol were less readily absorbed than 25% alcohol. Roth (26) found that when not more than 0.5 cc. of fluid of the digitalis preparation was injected into the ventral lymph sac, there was no difference in toxicity whether the solvent was alcoholic or aqueous. Edmunds, Lovell and Braden (9) removed all alcohol from preparations. They pointed out the need for standardization along these lines, having observed that some manufacturers allow 25% alcohol in their dilutions for injection. As a result of recent investigations Munch and Quici (20) claim that an alcohol content up to 30% of the fluid to be injected produces no essential or consistent differences in the assay on frogs, so that it is unnecessary to concentrate and redilute tinctures of digitalis in making assays according to the methods of the present Pharmacopœia. In the standard method of the Geneva Conference (22) most of the alcohol of the preparation is removed by evaporation and replaced with distilled water, while the U. S. P. X (33) allows a maximum of 20% alcohol, dilutions being made with distilled water. It will be observed that neither the U. S. P. X nor Geneva Conference methods specify an exact amount of alcohol in the fluid to be injected.

*9. Length of the Observation Period.*—Most of the frog methods for the assay of digitalis employ one of two end-points, either (*a*) systolic standstill of the ventricle or (*b*) death. The smallest amount of the drug producing the effect in (*a*) is known as the minimum systolic dose (M. S. D.) in (*b*) as the minimum lethal dose (M. L. D.). Various methods of assay by the lymph sac (and other) methods employ different lengths of time in which these end-points may appear. Houghton (16, 17) advocated a minimum lethal dose frog method with an observation period of twelve hours which in modified form appears to be preferred by others, especially European investigators (3, 6, 22, 23, 24, 25, 30, 31, 32). Famulener and Lyons (10) originated the one-hour minimum systolic dose method in the United States, where it has been most popular since its introduction thirty years ago and, in a modified form, has been the standard for a decade and a half. Probably the main objections which are raised against the one-hour lymph sac method are based on

complaints similar to those of Rowe (23, 24, 25), that not enough time is allowed for absorption, and that systolic standstill at any time previous to death is not an accurate end-point. Edmunds, Lovell and Braden (9) maintain that the one-hour method is satisfactory for digitalis, but that a longer observation period is necessary for the strophanthins. While the U. S. P. X one-hour method (33) presents obvious advantages over other frog heart-lymph sac methods in economy of time, the question is still debatable as to whether a longer period of observation such as four hours, as specified in the Geneva Conference Method (22), might not lead to more accurate results. The length of the observation period is closely allied with the factor of absorption, which is discussed below.

*10. Absorption.*—Absorption of digitalis from the lymph sac depends on many factors, such as the species, sex, size and health of the frogs, the character of the solvent, the concentration of the active drug, the age of the preparation, the season of the year, the temperature of the assay, the amount of fluid injected and the length of time allowed for absorption, most of which have been discussed above. Focke (11) using his short time method and injecting into the leg lymph sacs, observed systolic standstill from greatly different doses, which he attributed to variable absorption. Hale (13) asserted that "red leg" and poor health delayed absorption. As a result of comprehensive studies on absorption from the lymph sac, Baker (2) concluded that (*a*) the majority of healthy frogs will absorb 0.015 cc. of fluid per Gm. of body weight in one hour; (*b*) poor absorption is most likely to occur in the spring and late autumn; (*c*) light appears favorably to influence absorption; and (*d*) while absorption apparently is not affected by "red leg" disease, it is largely dependent on the health of the frogs and the conditions under which they are kept and handled. Roth (26), using 25% alcoholic solutions, found that the absorption and toxicity of digitalis bodies increased with the temperature; that while females showed a more variable absorption than males, the occurrence of eggs bore no relation to the degree of absorption. Paranjpe (21) found a wide variation in absorption with 25% alcoholic solutions of digitalis bodies from the lymph sacs of 40-Gm. frogs. Haskell (15) observed that as tinctures aged, their absorbability decreased. Smith and McClosky (27), while finding no constant relationship between the presence of unabsorbed fluid in the lymph sac, the condition of the heart and the size of the dose, agree that the extreme variations in susceptibility are largely accounted for by lack of absorption. Rowe (24, 25) claimed that the irritation produced by digitalin caused the secretion of a large amount of fluid into the lymph sac, thereby lengthening the time of absorption. Edmunds, Lovell and Braden (9) found that digitalis was more readily absorbed from the lymph sac than was strophanthin.

## EXPERIMENTAL.

In the autumn of 1931 while making an assay of a tincture of digitalis by the U. S. P. X method, it was observed that absorption from the lymph sac was complete in only four out of twenty frogs. Further, observation showed that absorption was complete in two of three females, but in only two of seventeen males. These results led to a number of assays by various frog methods, the essentials of which are described on next page.

METHODS.

(*1*) *The U. S. P. One-Hour Frog Heart-Lymph Sac Method.*—This method (33) requires the use of healthy grass frogs, *Rana pipiens*, twenty to thirty Gm. in weight. They must be stored in a cool place in running water, where the temperature preferably does not rise above 15° C. The day before the frogs are to be used, they are placed in a tank containing water at a temperature of approximately 20° C. One hour before the assay, they are weighed to within 0.5 Gm. and placed in water at a depth of about one cm., which is kept at a constant temperature of 20° C. during the assay. The dose of the tincture is calculated according to the weights of the frogs, and is injected into the ventral lymph sac through the floor of the mouth, the amount of fluid being about 0.015 cc. per Gm. of body weight. Dilutions are made with distilled water, and partial evaporation of the tincture is necessary in those cases where the alcohol content of the dilutions would otherwise exceed 20%. Fifth-eight minutes after the injection each frog is pithed; the heart is later exposed and examined at the end of one hour. The correct end-reaction at this time is systolic standstill of the ventricle, with the auricles widely dilated. The amount producing this effect is known as the minimum systolic dose (M. S. D.). If any of the injected drug is found unabsorbed in the lymph sac, the results with the animal must be rejected in recording the assay.

(*2*) *The Modified U. S. P. Four-Hour Method.*—This assay differs from the U. S. P. X method only in that four hours instead of one are allowed for the absorption of the drug.

(*3*) *The Intramuscular Frog Method of Dooley and Higley.*—In this method (7) grass frogs, *Rana pipiens*, are used as in the U. S. P. X method. All the alcohol of the preparation is evaporated at a temperature not over 50° C. and enough alcohol is added to make 15% when the preparation is brought up to the original volume with physiological saline (0.7%). Dilutions of this modified tincture are made so that the amount of fluid injected is never more than 0.01 cc. per Gm. of body weight. One-half of the total dose is injected diagonally into the thickest part of each thigh with a fine needle to avoid hemorrhage. Otherwise, the procedures and end-point are the same as those of the U. S. P. X method.

(*4*) *The Intravenous Frog Method of Smith and McClosky.*—This method (27) also employs the grass frog, *Rana pipiens*. All the alcohol is removed from the preparation by evaporation on a water-bath at a temperature not over 50° C., the evaporation not proceeding to dryness. The residue is taken up with enough physiological saline to make a concentration of twenty to forty mg. of digitalis per cc. After filtration, it is diluted with physiological saline, to from two and one-half to five times the original volume. The frog's brain is then pithed, the animal is fastened on its back and a median incision is made over the ventral lymph sac. The drug is slowly injected (tuberculin syringe, 26-gauge needle), into the right or left musculo-cutaneous vein, which is clamped after the needle is removed. The animal is then returned to the constant temperature tank, and at the end of one hour its cord is pithed and the examination is made in the usual manner. The end-point is the same as in the U. S. P. X method.

TINCTURES EXAMINED.

*Tincture "A:"* A composite tincture prepared by the class in pharmacology (24 preparations of 100 cc. each) during October 1931, differing from the U. S. P. X requirements only in that it was not defatted.

*Tincture "B:"* A defatted tincture made by the author according to the U. S. P. X during the first week of December 1931.

FROGS USED.

*Frogs "A:" Rana pipiens*, received September 1931, varying in weight from 36 to 69 Gm., stored in water in the basement at a temperature never over 15° C.

*Frogs "B:" Rana pipiens*, received during November 1931, varying in weight from 35 to 50 Gm., stored similarly to Frogs "A."

*Frogs "C:" Rana pipiens*, received April 1932, varying in weight from 24 to 67 Gm., stored in running water in the basement at about 15° C.

*Frogs "D:" Rana pipiens*, received May 1932, varying in weight from 24 to 44 Gm. stored in running water in the basement not over 18° C.

*Frogs "F:" Rana pipiens*, received May 31, 1932, varying in weight from 26 to 37 Gm., stored in running water in the basement not over 20° C.

PROCEDURE.

The assays on frogs "A" and "B" in the autumn were run at temperatures varying from 22.5° to 25.5° C. instead of at the standard of 20° C.

Frogs ranging in weight from 24 to 67 Gm. were used.

Frogs "C," "D" and "F" were placed in the constant temperature tank at 20° C. for one hour previous to and during the assay.

All animals were weighed to within one Gm. and the amount of fluid injected was adjusted so as to average about 0.5 cc., with a maximum of 0.7 cc. and a minimum of 0.3 cc. The amount of alcohol in the preparations injected ranged between zero and 20%.

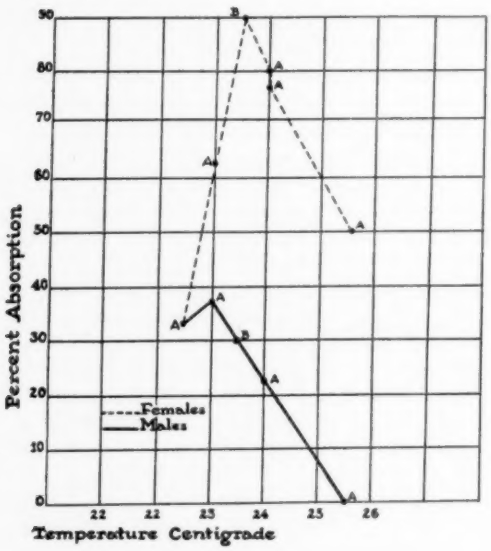


Fig. 1.—Absorption of digitalis tinctures "A" and "B" from the lymph sac of male and female frogs (*Rana pipiens*) at various temperatures by the U. S. P. one-hour method in the autumn of 1931. "- - - - - -" = females "———" = males.

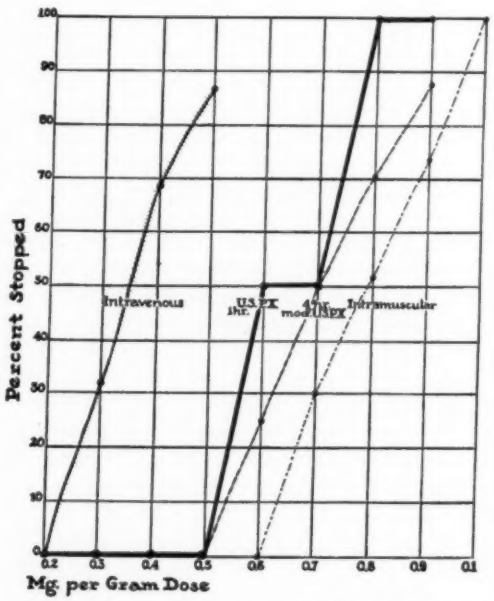


Fig. 2.—Comparison of systolic standstill doses of digitalis tincture "B" on male frogs (*Rana pipiens*) by four assay methods in the spring of 1932, at 20° C.

In the intravenous method of Smith and McClosky the modified diluted preparations were not filtered; in the intramuscular method of Dooley and Higley all of the alcohol was removed.

TABLE I.—THE INFLUENCE OF SEX ON ABSORPTION OF TINCTURE OF DIGITALIS FROM THE LYMPH SAC OF FROGS (*Rana Pipiens*), USING THE ONE-HOUR METHOD.

Tinctures: "A," "B" Temperature range 22.5° to 25.5° C.
Frogs: "A," "B" Date of tests: Autumn, 1931.

| | Number of Frogs Injected. | Number Showing Complete Absorption. | Percentage Absorption. |
|---|---|---|---|
| Males | 43 | 11 | 25.6 |
| Females | 54 | 36 | 66.6 |

Table I shows that absorption of modified tincture of digitalis from the ventral lymph sac in one hour was much better in female than in male grass frogs (*Rana pipiens*), in the autumn at temperatures ranging from 22.5° to 25.5° C., the ratio being over 2.5 to 1. At this season of the year all females contained egg-masses in about the same state of development; determinations made over this period on 33 females showed that the egg-masses averaged 20% of the weight of the frogs.

THE INFLUENCE OF TEMPERATURE ON ABSORPTION OF TINCTURE OF DIGITALIS FROM THE LYMPH SAC OF MALE AND FEMALE FROGS (*Rana Pipiens*), USING THE ONE-HOUR METHOD.

Figure 1 shows the per cent absorption in males and females plotted against the temperature, and indicates that the increased susceptibility at higher temperatures is at least due partly to the increased rate and degree of absorption. The only assay made with Tincture "B" fits perfectly with Tincture "A" in the graph, with both male and female frogs. It should be noted that while the temperatures are non-consecutive environmental variations, the resulting graphs are almost entirely uniform. It is also significant that in both sexes the best absorption appears between the ranges of 22.5° and 23.5° C.

TABLE II.—EFFECT OF ALCOHOL CONTENT OF MODIFIED TINCTURE OF DIGITALIS ON ABSORPTION IN MALE FROGS (*Rana Pipiens*).

Tinctures : "A," "B" Temperature: 20° C.
Frogs: "C," "D," "F" Date of Tests: Spring, 1932.

| Method of Assay. | Alcohol Per Cent. | Diluent. | Number of Frogs Injected. | Number Showing Complete Absorption. | Per Cent Showing Complete Absorption. |
|---|---|---|---|---|---|
| One-hour method | Not over 20% | 0.7% saline | 30 | 3 | 10 |
| One-hour method | None | ..... | 46 | 10 | 21.7 |
| Four-hour method | Not over 20% | ..... | 9 | 7 | 77.7 |
| Four-hour method | None | ..... | 52 | 50 | 96.2 |

Table II shows the relation between the alcohol content and the absorption of the modified tincture, using the one- and four-hour methods. In neither method does an alcohol content ranging from zero to 20% practically affect the degree of absorption.

TABLE III.—COMPARISON OF THE ABSORPTION OF TINCTURE OF DIGITALIS FROM THE LYMPH SAC OF MALE FROGS (*Rana Pipiens*), USING THE ONE-HOUR AND FOUR-HOUR METHODS.

Tincture "B" Temperature: 20° C.
Frogs: "C," "D," "F" Date of Tests: Spring, 1932.

| | One-Hour Method. | | Four-Hour Method. | |
|---|---|---|---|---|
| Dose Used (Mg. per Gm.). | Number of Frogs Injected. | Number Showing Complete Absorption. | Number of Frogs Injected. | Number Showing Complete Absorption. |
| 0.2 | 2 | 1 | .. | .. |
| 0.3 | 4 | 1 | .. | .. |
| 0.4 | 4 | 1 | .. | .. |
| 0.5 | 4 | 0 | 2 | 2 |
| 0.6 | 13 | 2 | 12 | 12 |
| 0.7 | 14 | 2 | 19 | 18 |
| 0.8 | 17 | 3 | 18 | 17 |
| 0.9 | 18 | 3 | 10 | 8 |
| Totals | 76 | 13 | 61 | 57 |
| Percentage | | 17.1 | | 93.4 |

Assays begun in the spring of 1932 with male *Rana pipiens* frogs showed such poor absorption by the one-hour method that it was decided to run parallel series of

assays in which the time allowed for absorption was increased from one to four hours. The results of this comparison are given in Table III. Absorption from the ventral lymph sac was complete in only 17.1% of 76 frogs by the one-hour method, while it was complete in 93.4% of 61 frogs by the four-hour method. (The relation of these two methods of assay to the minimum systolic dose will be discussed later.)

TABLE IV.—COMPARISON OF THE ASSAY OF THE TINCTURE OF DIGITALIS BY FOUR FROG METHODS, USING MALE GRASS FROGS (*Rana Pipiens*).

Tincture: "B" Temperature: 20° C.
Frogs: "C," "D," "F" Date of Tests: Spring, 1932.

| Dose Used (Mg. per Gm.). | One-Hour Method. Number of Frogs Showing Complete Absorption. | "+" | Four-Hour Method. Number of Frogs Showing Complete Absorption. | "+" | Intramuscular Method (Dooley-Higley). Number of Frogs Injected. | "+" | Intravenous Method (Smith-McCloskey). Number of Frogs Injected. | "+" |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 2 | 0 |
| 0.2 | 1 | 0 | | | | | 6 | 1 |
| 0.3 | 1 | 0 | | | | | 16 | 11 |
| 0.4 | 1 | 0 | | | | | 15 | 13 |
| 0.5 | 0 | 0 | 2 | 0 | 2 | 0 | | |
| 0.6 | 2 | 1 | 12 | 3 | 12 | 0 | | |
| 0.7 | 2 | 1 | 18 | 9 | 20 | 6 | | |
| 0.8 | 3 | 3 | 17 | 12 | 19 | 10 | | |
| 0.9 | 3 | 3 | 8 | 7 | 15 | 11 | | |
| 1.0 | | | | | 2 | 2 | | |

"+" indicates systolic standstill of ventricle.

Table IV indicates that the minimum systolic dose is between 0.7 and 0.8 mg. per Gm. by either the one-hour or the four-hour method (see also Fig. 2). It would appear from these results that the minimum systolic dose is practically the same by the one-hour and four-hour methods; however, the four-hour method gives more definite results with a smaller number of frogs, and therefore is more economical than the one-hour method. The slight divergence of the one-hour and four-hour curves between 0.7 and 0.8 mg. in Fig. 2 is of little significance since the number of frogs in which complete absorption was obtained was very small in the one-hour method.

Assays made on 70 frogs by the intramuscular method of Dooley and Higley (7) gave rather uniform results as shown in Table IV and Fig. 2, and indicate approximately the same minimum systolic dose as the one- and four-hour lymph sac methods, instead of the 18.6% smaller dose observed by Dooley and Higley (7).

Thirty-nine assays made by the intravenous method of Smith and McClosky (27) show a minimum systolic dose of 0.4 mg. per Gm., or about one-half that obtained by the three other methods, a finding which is in accord with the results of other investigators. The effective dose is sharply defined (Table IV) and the toxicity curve is remarkably uniform (Fig. 2).

## DISCUSSION.

The better absorption of modified tincture of digitalis by female frogs as compared with males is not easily accounted for, particularly in the autumn. The presence of the egg-mass may be accompanied by metabolic changes which affect absorption from the lymph sac, and it would appear that such influences exert a relatively marked effect in the spawning season (spring).

The influence of the weight of the egg-mass upon the size of the dose is probably an important factor. Observations made in the autumn showed that all the females contained masses of partially developed eggs, averaging 20% of the body weight. If the distribution of the absorbed digitalis in the egg-mass is proportional to that in the body tissues, no correction in dosage will be necessary. However, if the distribution in the egg-mass is greater or less than in the tissues, the smallest amount producing systolic standstill will not represent the true minimum systolic dose.

## CONCLUSIONS.

1. Absorption of tincture of digitalis preparations in the autumn is much better in female than in male frogs (*Rana pipiens*) at temperatures ranging from 22.5° to 25.5° C.

2. Within the temperature ranges of 22.5° to 25.5° C., absorption was best at 23° C.

3. It appears that "increased susceptibility" occurring with a rise of temperature may be due in many instances to the increased absorption.

4. Absorption of tincture of digitalis in the spring in male frogs (*Rana pipiens*) by the U. S. P. X method is much more complete when the period of observation is increased from one to four hours.

5. From a practical standpoint an alcohol content varying from zero to 20% produces no marked change in the rate or amount of absorption and toxicity.

6. During the spring months the minimum systolic dose of tincture of digitalis appears to be approximately the same with the one-hour, the four-hour and the intramuscular methods, while by the intravenous method of Smith and McClosky it is about half that of the three other methods.

7. The value of the U. S. P. X method would be augmented by limiting the assay to male frogs and by increasing the period of observation from one to four hours, both of which measures were recommended by the Geneva Conference (22) of the League of Nations in 1925.

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# A CHEMICAL EXAMINATION OF THE OIL OF ERGOT.*

BY GEORGE W. FIERO.

Oil of ergot is obtained by extracting the drug with petroleum ether prior to the preparation of fluidextract of ergot, U. S. P. X. The fatty oil used in this investigation was contributed by Parke, Davis & Co. It was very dark colored, had a slight green fluorescence and a rancid odor.

Five lots consisting of 10 litres each were saponified by refluxing each lot with 15 litres of a 70 p. c. alcohol solution containing two Kg. of potassium hydroxide (2350 Gm. of KOH, U. S. P. X which contains 15 p. c. of water). This quantity was based upon the saponification value (182) established by saponifying a sample according to the U. S. P. X process. An additional 10 p. c. of potassium hydroxide was allowed to insure complete saponification. After refluxing 8 hours, as much as possible of the alcohol was removed by distillation. Since the soapy mixture had a tendency to froth and foam, it was possible to obtain only approximately one-half of the total volume of alcohol, the balance remaining in the soap solution.

The saponified oil was dissolved in several volumes of water, and the solution shaken repeatedly with ethyl ether to remove the unsaponifiable matter.

* Part of a thesis submitted for the degree of Doctor of Philosophy, University of Wisconsin, 1932, and read by title before the Scientific Section of the A. PH. A. at the Toronto meeting. The thesis, deposited in the University Library, contains numerous details in tabulated form not here reported.

The aqueous solution was then acidified with cold, dilute sulphuric acid. Sufficient ether had been retained by the aqueous solution to dissolve the liberated fatty acids and form a layer above the water. The ethereal solution was removed, the ether distilled off and the fatty acids obtained in the form of a brownish gray solid. Notwithstanding the fact that sufficient sulphuric acid had been used to render the solution distinctly acid, it was found that the fatty acids contained considerable soap.[1] Purification was attempted by melting the acids and pouring them in a fine stream into dilute hydrochloric acid. The mixture was stirred constantly with a mechanical stirrer for one hour. The fatty acids were collected, remelted and poured into ice water with constant stirring, to remove the hydrochloric acid retained. Since they still contained considerable soap, the entire operation of melting the fatty acids, pouring into hydrochloric acid and then remelting and pouring into water was repeated. The fatty acids, however, still contained soap.

As a result of the saponification, the following products were obtained:

1. Unsaponifiable portion of the oil.
2. The free fatty acids.
3. The glycerin solution.

*1.* The *unsaponifiable portion* of the oil was turned over to Kurt Bonstedt for investigation.

*2. The Fatty Acids. I. Preliminary Separation of the Fatty Acids.*—The lead-alcohol method of Twitchel (1) was employed to separate the solid from the liquid fatty acids. One kilogram of the mixed fatty acids was dissolved in 6 litres of hot alcohol. A hot solution of 750 Gm. of lead acetate in 6 litres of alcohol was added and the mixture shaken. No precipitate formed until the liquid became cool. After standing two days at 10° to 15°, the mixture was filtered, and the residue washed with cool alcohol. The filtrate contained the unsaturated fatty acids as lead salts.

The residue was dissolved in boiling alcohol containing 0.6 p. c. acetic acid, and the solution filtered. There was but a trace of brown-colored residue which was washed with additional hot acetic acid-alcohol. After standing two days at 10° to 15°, the mixture was filtered, and the residue, consisting of the lead salts of the saturated fatty acids, was washed with cool alcohol.

*A. Saturated Acids.*—The lead salts of the saturated fatty acids were treated with dilute nitric acid, which liberated the fatty acids. The solution was shaken with ether, which dissolved the fatty acids, and the ethereal solution was shaken repeatedly with water in a separatory funnel until free from nitric acid. Upon evaporation of the ether, the saturated fatty acids were obtained as a faintly straw-colored, very hard mass. The yield was 315 Gm. or 31.5 p. c. of total fatty acids. Since the iodine number was found to be 3.9, the saturated fatty acids were shown to be contaminated with 4.3 p. c. of unsaturated fatty acid (calculated as oleic). This is equivalent to 14 Gm., reducing the total saturated fatty acids to 301 Gm. or 30.1 p. c. The mixture had a melting point of 53°.

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[1] Matthes and his co-workers (2, 3) have shown that this oil contains considerable ricinoleic acid. It is interesting to note that castor oil soap is readily soluble in castor oil and very difficult to remove (4).

*a. Fractional crystallization.* The fatty acids were dissolved in 10 parts of 95 p. c. alcohol and allowed to cool slowly. The solid fatty acids which separated were removed by filtration. Fractions were obtained at the following temperatures: 18° (fraction "A"), 16° (fraction "B"), 14° (fraction "C"), 12° (fraction "D"). Fractions "A" and "B" were immediately redissolved in alcohol and refractionated. The fractions are indicated by the following table:

| Fraction. | Temperature. | Weight—Gm. | Melting Point. |
|---|---|---|---|
| A-1 | 20° | 26.73 | 56.0° |
| A-2 | 12° | 5.56 | 56.5° |
| A-3 | 4° | 3.94 | 56.0° |
| B-1 | 20° | 11.11 | 56.5° |
| B-2 | 12° | 4.97 | 55.8° |
| B-3 | 4° | 3.14 | 55.0° |
| C | Not refract. | 11.80 | 55.0° |
| D | ... | ... | 55.0° |

No satisfactory separation was effected, probably due to the formation of eutectic mixtures of the fatty acids (5) or to the formation of ethylic esters (6).

*b. Fractional precipitation.* Fifty grams of the mixed solid fatty acids were dissolved in 750 cc. of alcohol and treated with a 10 p. c. solution of hydrous magnesium acetate in alcohol. The magnesium soaps did not begin to precipitate until 100 cc. of magnesium acetate solution had been added. After standing 12 hours, the magnesium soaps were separated by filtration, boiled with hydrochloric acid to liberate the fatty acids and the separated fatty acids dissolved in alcohol.

This solution was treated with 15-cc. portions of magnesium acetate solution, sufficient ammonium hydroxide being added after each precipitation to neutralize the acetic acid freed. The solution was stirred while the magnesium acetate was being added, allowed to stand for at least one hour and the magnesium soap separated by filtration. Fractions 1 to 6, inclusive, were obtained from this solution, No. 6 being the residue after removing the alcohol.

Fractions 7 to 15, inclusive, were obtained in the same manner from the filtrate obtained from the above-mentioned magnesium soaps precipitated with 100 cc. of magnesium acetate solution. Fraction 15 was the residue.

The melting points of the magnesium soaps are not satisfactory for identifying the fatty acids as becomes apparent from the following tabulation:

| | |
|---|---|
| Myristic acid m. p. 53.8° | Mg myristate m. p. 150.4° |
| Palmitic acid m. p. 62.6° | Mg palmitate m. p. 121–122° |
| Stearic acid m. p. 69.3° | Mg stearate m. p. 132° |

Therefore, the fractions were boiled with dilute hydrochloric acid, cooled, filtered and the residue washed with water. The freed acid was then recrystallized from alcohol. The following fractions of free fatty acid were thus obtained:

| Fraction. | Weight—Gm. | Melting Point. |
|---|---|---|
| 1 | 1.95 | 51.0–51.2° |
| 2 | 2.44 | 53.8–54.0° |
| 3 | 1.11 | 53.5–54.0° |
| 4 | 4.07 | 55.5–56.0° |
| 5 | 1.65 | Softened 30° |
| | | Melted 44° |

| | | |
|---|---|---|
| 6 | 12.10 | (Residue) |
| 7 | 1.60 | 55.5–55.7° |
| 8 | 2.10 | 43.0° |
| 9 | 1.20 | 42.0° |
| 10 | 5.20 | 55.5–56.0° |
| 11 | 7.15 | 56.0° |
| 12 | 0.33 | 58.5–58.7° |
| 13 | 0.50 | 24.0° |
| 14 | 1.00 | 60.5–60.7° |
| 15 | 6.80 | (Residue) |
| | 49.20 Gm. | |

*c. Fractional distillation of methyl esters.* The mixed solid fatty acids (185 Gm.) were refluxed with 370 cc. of methyl alcohol containing 9 cc. of concentrated sulphuric acid. The excess methyl alcohol was recovered by distillation, and the methyl esters were dissolved in ether. This ethereal solution was washed with water until free from mineral acid. The ethereal solution was then dried with anhydrous sodium sulphate, and the esters obtained by distilling the ether.

The methyl esters thus prepared were distilled in a modified Claissen flask on an oil-bath at a pressure of 8 mm. The following fractions were collected.

FRACTIONAL DISTILLATION I.

| Fraction. | Boiling Range. | Weight—Gm. | Melting Point. |
|---|---|---|---|
| I | 174–179° | 31.62 | 28.0–28.5° |
| II | 179–180° | 46.92 | 26.5–27.0° |
| III | (Bumped over) | 20.95 | ..... |
| IV | 181–182° | 27.05 | 24.8–25.2° |
| V | 183–188° | 21.14 | 24.0–24.2° |
| VI | 188–196° | 9.10 | 19.8–20.2° |
| VII | 196–200° | 5.76 | 28.5–29.5° |
| VIII | (Residue) | 9.06 | ..... |

The fractions were redistilled as follows: Nos. I and II were distilled to 178°; III and IV were then added to and distilled with 182°; V was added to and distilled with 186°; VI was added to and distilled with 190°; VII and VIII were added to and distilled with 200°. A second group of fractions was obtained as indicated by the following table:

FRACTIONAL DISTILLATION II.

| Fraction. | Boiling Range. | Weight—Gm. | Melting Point. |
|---|---|---|---|
| A | 173–174° | 28.18 | 28.2° |
| B | 175–178° | 75.06 | 25.8-26.3° |
| C | 178–182° | 20.71 | 23.0–23.2° |
| D | 182-186° | 19.26 | 20.5–21.8° |
| E | 186-194° | 11.46 | 22.5–23.0° |
| F | 194–200° | 6.81 | 23.0–23.5° |
| G | (Residue) | 7.92 | ..... |

The fractions were redistilled in a similar manner and the following fractions were obtained:

FRACTIONAL DISTILLATION III.

| Fraction. | Boiling Range. | Weight—Gm. | Melting Point. |
|---|---|---|---|
| 1 | 164–168° | 3.75 | 26.2–26.5° |
| 2 | 169–171° | 13.35 | 28.0–28.2° |

| Fraction. | Boiling Range. | Weight—Gm. | Melting Point. |
|---|---|---|---|
| 3 | 172–175° | 77.95 | 28.5–28.7° |
| 4 | 176–178° | 14.82 | 26.5–27.0° |
| 5 | 179–185° | 12.32 | 22.5–23.2° |
| 6 | 186–190° | 21.57 | 22.5–23.0° |
| 7 | 190–196° | 14.10 | 28.0–28.5° |
| 8 | 197-200° | 2.77 | 30.0–30.2° |
| 9 | 201–206° | 4.60 | 32.0–32.5° |
| 10 | (Residue) | 1.73 | ..... |

The quantitative separation of the solid fatty acids is very difficult when one considers that they differ only about 10 p. c. in molecular weight. Fractional distillation of the methyl esters, which is the most satisfactory method employed, does not yield pure fractions unless, possibly, after a large number of redistillations. The fractions obtained from ergot oil, in most cases, probably contained but two saturated fatty acids. Oleic ester, although its boiling point is near that of stearic, begins to distil below its boiling point in the presence of other methyl esters (7). Thus, small amounts of oleic ester were present in all samples except No. 1, as indicated by the iodine value. After saponification, myristic acid was isolated from No. 1, stearic acid from No. 9 and the residue, and palmitic acid from Nos. 1 to 7, inclusive. Arachidic acid was not detected. The isolation of small amounts of stearic acid in a mixture with palmitic, or vice versa, is quite difficult, since the two form an eutectic mixture (the so-called "margaric acid" is considered by some to be such a mixture).

Daturic acid was not obtained from any of the fractions. Indeed, the existence of this acid is doubted by many authorities. Jamieson's recent (1932) "Vegetable Fats and Oils" does not mention daturic (or margaric) acid, although other fatty acids are considered in detail.

The following table indicates the approximate quantitative composition of the fractions. The amount of oleic ester is calculated from the iodine value. Lead oleate is less soluble in alcohol than lead linoleate or ricinoleate, hence the iodine value of the solid acids separated by the lead-salt-alcohol method is probably due to oleic acid. The amount of saturated ester may be approximated by the molecular equivalent (based upon the saponification value), after subtracting the oleic acid content.

| | M. E. | Weight—Gm. | I. V. | Fatty Acid. | P. C. | Weight—Gm. |
|---|---|---|---|---|---|---|
| 1. | 253.2 | 3.75 | 0.0 | Myristic | 44.3 | 1.66 |
| | | | | Palmitic | 55.7 | 2.09 |
| 2. | 265.9 | 13.35 | 2.5 | Myristic | 16.6 | 2.22 |
| | | | | Palmitic | 80.5 | 10.74 |
| | | | | Oleic | 2.9 | 0.39 |
| 3. | 267.0 | 77.95 | 2.8 | Myristic | 13.6 | 10.60 |
| | | | | Palmitic | 83.1 | 64.75 |
| | | | | Oleic | 3.3 | 2.60 |
| 4. | 270.0 | 14.82 | 4.3 | Myristic | 5.0 | 0.74 |
| | | | | Palmitic | 90.0 | 13.44 |
| | | | | Oleic | 5.0 | 0.74 |
| 5. | 273.0 | 12.32 | 6.0 | Palmitic | 86.2 | 10.41 |
| | | | | Stearic | 6.8 | 0.84 |
| | | | | Oleic | 7.0 | 0.87 |
| 6. | 276.0 | 21.57 | 9.0 | Palmitic | 79.9 | 17.25 |
| | | | | Stearic | 9.6 | 2.06 |
| | | | | Oleic | 10.5 | 2.26 |

| | | | | | |
|---|---|---|---|---|---|
| 7. | 279.5 | 14.10 | 13.2 | Palmitic | 61.7 | 8.70 |
| | | | | Stearic | 22.9 | 3.23 |
| | | | | Oleic | 15.4 | 2.17 |
| 8. | 292.5 | 2.77 | 20.4 | Palmitic | 17.8 | 0.49 |
| | | | | Stearic | 58.4 | 1.65 |
| | | | | Oleic | 23.8 | 0.63 |
| 9. | 295.0 | 4.60 | 26.2 | Palmitic | 4.9 | 0.23 |
| | | | | Stearic | 64.4 | 2.96 |
| | | | | Oleic | 30.7 | 1.41 |

165.23 Gm.

Summary of Solid Fatty Acids.

| | | |
|---|---|---|
| Myristic acid | 15.32 Gm. | 9.9 p. c. |
| Palmitic acid | 78.00 Gm. | 83.1 p. c. |
| Stearic acid | 10.74 Gm. | 7.0 p. c. |

or

| | |
|---|---|
| Myristic acid | 3.0 p. c. of total fatty acids |
| Palmitic acid | 25.0 p. c. of total fatty acids |
| Stearic acid | 2.1 p. c. of total fatty acids |

*B. Unsaturated Acids.*—The alcoholic solution of lead salts of the unsaturated fatty acids (see above) was concentrated to one-half of its volume and treated with hydrogen sulphide until no more lead sulphide precipitated. The mixture was then warmed to coagulate the lead sulphide and filtered. The residue was washed with alcohol, and the mixed filtrates concentrated in an atmosphere of carbon dioxide. The unsaturated fatty acids remained as a yellow-colored, oily liquid. Yield—624.5 Gm. or 62.45 p. c. of total fatty acids.

The unsaturated fatty acids were separated from each other according to the method of Rosenthaler (8). They were dissolved in ten volumes of glacial acetic acid and two volumes of ether. At a temperature not exceeding 8°, this solution was treated with a solution consisting of one part of bromine and two parts of glacial acetic acid until the bromine was in excess.

The mixture was then kept at 5° for 6 hours, and the precipitate removed by decantation and filtration. This precipitate, a brownish gray solid, proved to be alpha-linolenic hexabromide, m. p. 181°. It was present in very small quantities, only 0.12 Gm. being obtained, corresponding to 0.006 p. c. of the total liquid acids.

The filtrate was added to five volumes of water. A red, oily liquid separated to the bottom. The water was decanted and shaken out with ether. The separated oily liquid was then dissolved in the ethereal solution, dried with anhydrous sodium sulphate and the ether recovered. The residue consisted of 1032 Gm. of red, oily liquid.

This liquid was dissolved in one litre of petroleum ether, allowed to stand at 0° for several hours and filtered. A small amount of black residue was obtained. The filtrate was then diluted with two litres of petroleum ether and allowed to stand over night at −3° to −6°. A small quantity of dark brown, viscous, oily liquid separated to the bottom. After separation of this layer, the petroleum-ether solution was washed thoroughly with water to remove the trace of acetic acid which was retained by the ether solution (see above). After standing at −3° to −6° for several days, more oily liquid separated, making a total of 163 Gm. This liquid,

according to Matthès and Schuetz (2), is dibromricinoleic acid. The 163 Gm. of dibromide correspond to 89.7 Gm. of ricinoleic acid.

The oily liquid was debrominated with zinc, saponified with potassium hydroxide, and neutralized with hydrochloric acid to yield the free fatty acid. This acid was then exactly neutralized with sodium hydroxide, and treated with an excess of 1.5 p. c. ice cold potassium permanganate solution. The excess permanganate was reduced with sulphur dioxide which also liberated the free fatty acids. Two trihydroxides were obtained, melting at 110° and 115°. Matthes and Kuerschner (3) obtained these two trihydroxides from ricinoleic acid from ergot oil in addition to one melting at 140–142°.

The petroleum-ether solution, after separation of dibromricinoleic acid, was concentrated and allowed to stand for 24 hours at 0° to −6°. A solid, yellow-colored precipitate formed which melted at 103°. After crystallization from petroleum ether, it melted at 113° (uncorr.). The original petroleum-ether solution was allowed to stand again for 24 hours, and additional yellowish white crystals separated. These melted at 113°. These indicated alpha-linoleic tetrabromide, m. p. 114°. The yield, 21.14 Gm., corresponds to 7.47 Gm. of linoleic acid.

The filtrate was again concentrated and allowed to stand for several days at 0° to −23°. A yellow, fatty substance (m. p. 57°) separated. This substance was separated, dissolved in acetone, and cooled with freezing mixture, when linoleic tetrabromide (m. p. 114°) separated. This was filtered and the mother liquid evaporated. The oily residue was dissolved in petroleum ether from which a red, oily liquid (ricinoleic dibromide) separated on cooling. The acid value (585) indicated that the yellow substance was a mixture of 90 p. c. linoleic and 10 p. c. ricinoleic bromides.

The filtrate from which the yellow solid originally separated was evaporated. The residue consisted of 391 Gm. of an oily liquid. Oxidation with dilute permanganate, after first debrominating with zinc (see oxidation of ricinoleic acid, above), yielded a dihydroxystearic acid which melted at 135° (dihydroxystearic acid from oleic acid melts at 133° to 136.5° (9)).

Thus it was found that the unsaturated fatty acids consisted of linolenic, linoleic, ricinoleic and oleic acids. The amount of linolenic was so small that for practical purposes it may be considered negligible so that the actual quantities of the other acids may be computed without it.

The acetyl value of the mixed fatty acids (59.1) indicates 35.8 p. c. of ricinoleic acid. Since the fatty acids contained 69.9 p. c. of liquid (unsaturated) fatty acids (after accounting for those which separated with the solid acids), 34.1 p. c. of the unsaturated fatty acids consisted of oleic and linoleic. The iodine value of the mixed fatty acids (73.5) indicates an iodine value of 105 for the unsaturated fatty acids. After accounting for the ricinoleic acid, the quantities of oleic and linoleic may thus be calculated. The approximate quantitative composition of the unsaturated fatty acids is indicated in the following table:

| | |
|---|---|
| Oleic acid | 30 p. c. of the unsaturated acids |
| Ricinoleic acid | 51 p. c. of the unsaturated acids |
| Linoleic acid | 19 p. c. of the unsaturated acids |
| Linolenic acid | Traces |

or

| | |
|---|---|
| Oleic acid | 20.9 p. c. of total fatty acids |
| Ricinoleic acid | 35.8 p. c. of total fatty acids |
| Linoleic acid | 13.2 p. c. of total fatty acids |
| Linolenic acid | Traces |

*II. Study of About 18 Kilos of Fatty Acids. A. By Fractional Crystallization.*—The fatty acids were crystallized from a relatively concentrated (25 to 33 p. c.) alcoholic solution at various temperatures. The various fractions were then recrystallized from a more dilute solution in acetone, since a certain amount of ethyl ester was produced when alcohol was used. It was found, however, that solid fatty acids could not be satisfactorily separated from the liquid acids by this method.

*B. By Fractional Distillation of Methyl Esters.*—The fatty acids were then esterified with methyl alcohol and submitted to the fractional distillation process of Gruen and Janko (10). This consists in treating the methyl esters (in petroleum ether or chloroform solution) with bromine solution at 0° to 5°. After the fatty acids are entirely brominated, the mixture was washed with aqueous sodium bicarbonate solution and dried with anhydrous sodium sulphate.

The solvent was recovered, and the methyl esters subjected to fractional distillation at a pressure of 8 to 15 mm. There was considerable decomposition as was indicated by clouds of more volatile material produced below the boiling point of the esters. The first fractions obtained were straw colored, but after redistillation they were colorless. The iodine value, however, ranged from 15 to 50 indicating the presence of unsaturated fatty acids. This method was not satisfactory, possibly due to the oxidized condition of the original fixed oil.

## SUMMARY.

The solid fatty acids may be separated from each other more satisfactorily by fractional distillation of the methyl esters than by either fractional crystallization from alcohol or by fractional precipitation with magnesium acetate.

The approximate quantitative composition of the mixed fatty acids from the fatty oil of ergot is herewith tabulated:

| | P. C. of Total Fatty Acids. |
|---|---|
| Myristic acid | 3.0 |
| Palmitic acid | 25.0 |
| Stearic acid | 2.1 |
| Oleic acid | 20.9 |
| Ricinoleic acid | 35.8 |
| Linoleic acid | 13.2 |
| Linolenic acid | Traces |

## REFERENCES.

(1) Twitchel, *Ind. & Eng. Chem.*, 13 (1921), 806.
(2) Matthes and Schuetz, *Arch. Pharm.*, 265 (1927), 541.
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(4) Shrader, U. S. Dept. Agriculture, *Bull.* 687.
(5) Leathes, *The Fats*, page 5.
(6) Lewkowitsch, *Chem. Tech. and Anal. of Oils, Fats and Waxes*, 5th Edition, Vol. 1, page 663.

(7) Jamieson, *Vegetable Oils and Fats*, page 295.
(8) Rosenthaler, *Chem. Investigation of Plants*, page 83.
(9) Lewkowitsch, *loc. cit.*, Vol. 1, page 228.
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# A CHEMICAL STUDY OF MA HUANG.*[1]

BY ALICE H. HAYDEN[2] AND C. B. JORDAN.

## HISTORICAL.

Ma Huang presents one of the most interesting histories found in drug lore. Its antiquity, its varied rôles throughout the centuries and its recent spectacular rise to its present position in modern medicine weave a fascinating story for those interested in drugs and the relationship of pharmacognosy and chemistry to the development of medical science.

Early Chinese records (1) indicate that Ma Huang was known and used as early as the third century, B. C. The Chinese employed the drug to allay coughing, to promote sweating, to stimulate heart action, to relieve post-partem difficulties and to control fevers. Chen (2) reports that Ma Huang was usually prescribed with other crude drugs and made into a decoction and taken by the patient as such.

Ma Huang means astringent yellow. The taste is very astringent; this has been attributed to a high tannin content. There seems to be some doubt, however, as to just what is the exact application of the word "Huang" or "yellow." Some writers, Chen (3) and Nielsen (4), believe that the word yellow applies to the appearance of the dried stem, but Read (5) is of the opinion that the early literature refers to "Huang" as the color of the flower.

Ma Huang belongs to the seventh division of the Gymnospermous plants, the Gnetales. The exact botanical identity of this drug has been a subject of much confusion and discussion. The earlier investigators referred to it as *Ephedra vulgaris*, **var,** *helvetica*. However, recent investigations indicate that this term is now obsolete and should be dropped. The modern tendency is to consider Ma Huang as a generic term applying to various ephedrine-bearing species of Ephedra growing in China (5).

The drug is imported in large bales. There is no true grading of the product; oftentimes a single bale will contain several species of Ephedra. During the processes of collecting, drying, compressing and transporting, the plants become badly broken and most of the berries, flowers and bracts drop off so that a complete separation of the different species is practically impossible.

As far as can be ascertained, the first chemical investigation of the plant was carried out by Yamanshi, who, in 1885, isolated an alkaloid in an impure state. After the death of the discoverer, Nagai (1887) (6) with the assistance of Hori, continued the study, purified the product and named it ephedrine. It is interesting to note, however, that the term ephedrine was first used by Loew (1875) to desig-

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* Scientific Section, A. PH. A., Toronto meeting, 1932.

[1] An abstract based upon a thesis by Alice H. Hayden submitted to the Faculty of Purdue University in partial fulfilment of the requirements for the degree of Doctor of Philosophy. The original thesis is accompanied by a bibliography of over one thousand references.

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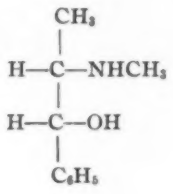
nate a red, amorphous powder obtained from the tannin of an American species of Ephedra (7). The name ephedrine has also been applied to an alkaloid obtained from *Ephedra monostachya*, but investigations show that this compound is not identical with the *l*-ephedrine obtained from Ma Huang. The word ephedrine is now used only in the sense in which Nagai employed it—to designate *l*-ephedrine:



The history of ephedrine is comparable with the histories of several other of our important drugs and chemicals. This compound, like cocaine, carbon tetrachloride and phenolphthalein, was known for a long time before its most valuable medicinal properties were realized and investigated. Miura (8) (1887) subjected Nagai's ephedrine to physiologic investigations and demonstrated its mydriatic effect. The greatest pharmacologic properties of the drug were overlooked owing to the fact that early workers failed to use anything but toxic doses. Consequently, ephedrine was little used for purposes other than ophthalmologic for many years. Some experiments demonstrating the essentially sympathomimetic effects of ephedrine were conducted as early as 1917 (9), but the real therapeutic possibilities of this compound were not recognized until 1923 when Chen re-isolated the alkaloid.

There have been many studies of Ma Huang and its alkaloids but, as far as we have been able to ascertain, no complete, systematic chemical examination of this ancient remedy has been executed. We are therefore submitting the following data regarding this drug.

## GENERAL ANALYSES.

### I. Determination of Volatile Constituents.

TABLE I.

| Sample No. | Determination No. | Moisture in %. Sample. | Moisture in %. Average. | Other Volatile Constituents. Sample. | Other Volatile Constituents. Average. | Total Volatile Constituents. Sample. | Total Volatile Constituents. Average. |
|---|---|---|---|---|---|---|---|
| | 1 | 3.62 | | 1.07 | | 4.69 | |
| I | 2 | 3.66 | 3.64 | 1.11 | 1.086 | 4.77 | 4.726 |
| | 3 | 3.64 | | 1.08 | | 4.72 | |
| | 1 | 3.71 | | 1.11 | | 4.82 | |
| II | 2 | 3.78 | 3.75 | 1.08 | 1.083 | 4.86 | 4.838 |
| | 3 | 3.76 | | 1.06 | | 4.82 | |
| | 1 | 4.02 | | 1.21 | | 5.23 | |
| III | 2 | 4.04 | 4.013 | 1.19 | 1.193 | 5.22 | 5.206 |
| | 3 | 3.98 | | 1.18 | | 5.17 | |
| | 1 | 4.26 | | 1.24 | | 5.50 | |
| IV | 2 | 4.30 | 4.293 | 1.18 | 1.21 | 5.48 | 5.503 |
| | 3 | 4.32 | | 1.21 | | 5.53 | |

II. Extraction of Samples with Various Solvents.

TABLE II.

| Solvent. | Sample No. | Determination No. | Weight of Sample. | % Extractive. Individual. | Average. |
|---|---|---|---|---|---|
| Petroleum ether | I | 1 | 9.78159 | 1.55 | |
| | | 2 | 9.84735 | 1.59 | 1.57 |
| Ether | | 1 | | 1.36 | |
| | | 2 | | 1.34 | 1.35 |
| Chloroform | | 1 | | 0.588 | |
| | | 2 | | 0.572 | 0.58 |
| Ethyl acetate | | 1 | | 4.41 | |
| | | 2 | | 4.53 | 4.47 |
| Ethyl alcohol | | 1 | | 10.35 | |
| | | 2 | | 10.20 | 10.275 |
| Water | | 1 | | 9.46 | |
| | | 2 | | 9.25 | 9.355 |
| Residue | | 1 | | 72.47 | |
| | | 2 | | 72.16 | 72.315 |
| | | | | | 99.915 |
| Petroleum ether | II | 1 | 9.94740 | 1.64 | |
| | | 2 | 9.64845 | 1.66 | 1.65 |
| Ether | | 1 | | 1.32 | |
| | | 2 | | 1.37 | 1.345 |
| Chloroform | | 1 | | 0.65 | |
| | | 2 | | 0.69 | 0.67 |
| Ethyl acetate | | 1 | | 4.81 | |
| | | 2 | | 4.63 | 4.72 |
| Ethyl alcohol | | 1 | | 11.28 | |
| | | 2 | | 11.17 | 11.225 |
| Water | | 1 | | 10.33 | |
| | | 2 | | 10.46 | 10.395 |
| Residue | | 1 | | 70.11 | |
| | | 2 | | 70.26 | 70.185 |
| | | | | | 100.19 |

Several American species were available to us, and, by way of comparison, the following extractions were made:

TABLE III.

| Solvent. | Ma Huang. Individual. | Average. | *E. nevadensis.* Individual. | Average. | *E. antisyphilitica.* Individual. | Average. |
|---|---|---|---|---|---|---|
| Petroleum ether | 1.68 | | 1.72 | | 0.98 | |
| | 1.64 | 1.66 | 1.74 | 1.73 | 0.96 | 0.97 |
| Ether | 0.93 | | 0.82 | | 1.01 | |
| | 0.87 | 0.90 | 0.93 | 0.87 | 1.64 | 1.32 |
| Ethyl alcohol | 17.04 | | 14.09 | | 12.61 | |
| | 16.83 | 16.93 | ..... | 14.09 | 12.06 | 12.33 |
| Water | 9.70 | | 4.07 | | 3.52 | |
| | 9.25 | 9.47 | ..... | 4.07 | ..... | 3.52 |

III. Ash Determination.

TABLE IV.

| Sample No. | Determination No. | Total Ash. Individual. | Average. |
|---|---|---|---|
| I | 1 | 8.59 | |
| | 2 | 8.66 | 8.626 |
| | 3 | 8.63 | |
| II | 1 | 8.42 | |
| | 2 | 8.39 | 8.393 |
| | 3 | 8.37 | |
| III | 1 | 7.92 | |
| | 2 | 7.78 | 7.85 |

IV. Analysis of Ash.

TABLE V.

| Analysis for | Determination No. | % of Ash. Individual. | Average. |
|---|---|---|---|
| Water-soluble ash | 1 | 21.638 | |
| | 2 | 20.782 | 21.262 |
| | 3 | 21.365 | |
| HCl-soluble ash | 1 | 59.388 | |
| | 2 | 59.824 | 60.965 |
| | 3 | 63.684 | |
| Insoluble ash | 1 | 18.972 | |
| | 2 | 19.381 | 17.764 |
| | 3 | 14.940 | |

Liu and Read (10) have called attention to the high insoluble ash content of *E. sinica*. They have included this characteristic as one of the methods of differentiation of the several Chinese Ephedras: *E. sinica*, *E. distachya* and *E. equisetina*.

Chen (11) ran qualitative and quantitative tests on the ash. His tests showed the presence of chlorine, sulphur, phosphorus, calcium, potassium, sodium and small quantities of manganese and iron. We have found that magnesium is also present in the ash.

V. Crude Fibre Determination.[1]

TABLE VI.

| Sample No. | Determination No. | Crude Fibre. Individual. | Average. |
|---|---|---|---|
| I | 1 | 19.48 | |
| | 2 | 19.55 | 19.513 |
| | 3 | 19.51 | |
| II | 1 | 22.25 | |
| | 2 | 22.31 | 22.286 |
| | 3 | 22.30 | |
| III | 1 | 24.11 | |
| | 2 | 24.20 | 24.163 |
| | 3 | 24.16 | |

[1] U. S. P. Methods.

VI. Ether-Soluble Extractive.[1]

TABLE VII.

| Sample. No. | Determination No. | Non-Volatile Ether. Individual. | Average. | Volatile Ether. Individual. | Average. |
|---|---|---|---|---|---|
| | 1 | 7.31 | | 0.67 | |
| I | 2 | 7.22 | 7.266 | 0.71 | 0.693 |
| | 3 | 7.27 | | 0.70 | |
| | 1 | 6.75 | | 0.73 | |
| II | 2 | 6.81 | 6.783 | 0.75 | 0.736 |
| | 3 | 6.79 | | 0.73 | |
| | 1 | 7.93 | | 0.55 | |
| III | 2 | 8.11 | 8.003 | 0.52 | 0.523 |
| | 3 | 7.97 | | 0.50 | |

VII. Alcohol Extractives.[1]

TABLE VIII

| Sample. No. | Determination No. | Alcohol. Individual. | Average. | Dilute Alcohol. Individual. | Average. |
|---|---|---|---|---|---|
| I | 1 | 17.73 | | 20.10 | |
| | 2 | 17.82 | 17.775 | 19.88 | 19.99 |
| II | 1 | 18.10 | | 19.75 | |
| | 2 | 17.89 | 17.995 | 19.77 | 19.73 |
| III | 1 | 16.38 | | 21.42 | |
| | 2 | 16.65 | 16.815 | 21.49 | 21.455 |

VIII. Water-Soluble Extractive.[1]

TABLE IX.

| Sample. No. | Determination No. | Water Extract. Individual. | Average. |
|---|---|---|---|
| I | 1 | 10.37 | |
| | 2 | 10.44 | 10.405 |
| II | 1 | 10.70 | |
| | 2 | 10.76 | 10.73 |
| III | 1 | 14.89 | |
| | 2 | 15.23 | 15.06 |

IX. Extractive Soluble in Purified Petroleum Benzin.[1]

TABLE X.

| Sample. No. | Determination No. | Benzin Extract. Individual. | Average. |
|---|---|---|---|
| I | 1 | 1.99 | |
| | 2 | 2.21 | 2.10 |
| II | 1 | 2.33 | |
| | 2 | 2.28 | 2.305 |
| III | 1 | 2.44 | |
| | 2 | 2.68 | 2.56 |

SPECIFIC ANALYSES.

*Assays for Total Alkaloids.*—Various optical, colorimetric, volumetric, gravimetric and biological assays have been devised for the determination of the total

[1] U. S. P. Methods.

alkaloids in ephedrine-bearing drugs and preparations. The yields obtained by different investigators are widely divergent. Generally, the earlier workers obtained lower results than the more recent investigators. Studies of the different assay processes have accounted for some of these variations, and from recent botanical studies, we now know that there are several species of Ephedra upon the market as Ma Huang and that some of these contain lower percentages of alkaloids than others. Some species also yield a higher percentage of *l*-ephedrine than do others. We have undertaken a special study of these methods in order to determine, if possible, the most accurate and satisfactory means of assay.

There are several factors to be taken into consideration in a study of this problem:

1. The alkaloid, ephedrine, has a melting point of 40° C. and is somewhat volatile.
2. Ephedrine is soluble in ether, chloroform, petroleum ether, alcohol and water.
3. The isomers, ephedrine and pseudoephedrine, are intraconvertible. A high total yield of alkaloids is not necessarily indicative of a high *l*-ephedrine content.
4. Chloroform reacts with ephedrine under certain conditions to form the hydrochloride. According to Peterson (12) this reaction is accompanied by the formation of benzaldehyde.

We have assayed two different samples of Ma Huang according to the following methods:

1. Assay of Ephedrine by U. S. P. IX Method for Belladonna Root (13).
2. Assay of Ephedrine by U. S. P. X Method for Belladonna Root (14).
3. J. B. Williams' (15) modification of the U. S. P. X Method.
4. Feng and Read (16) Direct Alkalinization Method.
5. Feng and Read (16) Hot Acid Extraction Method.
6. Paul and Glycart Assay (17).
7. Hsu's Method (18).
8. Barium Hydroxide Method.

The Barium Hydroxide Method of assay is as follows:

Dissolve 10 Gm. of barium hydroxide in 75 cc. of distilled water and mix thoroughly with 20 Gm. of the crude drug. Allow to macerate for two hours. Transfer the material to a percolator and pour on 100 cc. of an alcohol-ammonium chloride solution (2% ammonium chloride in diluted alcohol—95% alcohol 70, water 30), and allow to macerate for 12 hours. Allow the percolation to proceed at its normal rate until 500 cc. of the same menstruum have been added. Heat the percolate on a water-bath until the alcohol has been evaporated. Shake out the alkaloids with three successive portions of chloroform, using 50, 40 and 30 cc., respectively, and filter these extractions through a pledget of cotton moistened with chloroform. Filter the aqueous extract and rinse the marc with dilute ammonia. Add 10 cc. of stronger ammonia to the aqueous liquid and again extract with chloroform until a portion of the residue no longer gives a positive "Biuret" (19) test with dilute copper sulphate and sodium hydroxide. Combine the chloroformic extracts and allow to evaporate spontaneously. Dissolve the residue in a little neutral alcohol, add 20 cc. of 0.1*N* HCl and titrate the excess with 0.02*N* NaOH, methyl red being used as an indicator.

The following results were obtained using the different methods of assay for the two samples of Ma Huang:

| Method. | Sample I. Individual. | Sample I. Average. | Sample II. Individual. | Sample II. Average. |
|---|---|---|---|---|
| U. S. P. IX Assay (13) | 0.864 | | 0.735 | |
| | 0.851 | 0.8575 | 0.721 | 0.728 |
| U. S. P. X Assay (14) | 0.854 | | 0.722 | |
| | 0.841 | 0.8475 | 0.703 | 0.7125 |

| Method. | Sample I. Individual. | Average. | Sample II. Individual. | Average. |
|---|---|---|---|---|
| Williams' Modification (15) | 0.972 | | 0.840 | |
| U. S. P. X Method | 0.961 | 0.966 | 0.819 | 0.8295 |
| Feng and Read Direct | 1.13 | | 1.01 | |
| Alkalinization Method (16) | 1.26 | 1.195 | 0.969 | 0.9895 |
| Feng and Read Hot Acid (16) | 1.41 | | 1.17 | |
| Extraction Method | 1.33 | 1.37 | 1.18 | 1.175 |
| Paul and Glycart Assay (17) | 1.10 | | 0.878 | |
| Titration Procedure No. 1 | 1.03 | 1.065 | 0.859 | 0.868 |
| Titration Procedure No. 2 | 1.04 | | 0.880 | |
| | 1.11 | 1.075 | 0.883 | 0.881 |
| Hsu's Method (18) | 1.88 | | 1.61 | |
| | 1.83 | 1.855 | 1.65 | 1.63 |
| Barium Hydroxide Method | 2.10 | | 1.83 | |
| | 2.04 | | 1.88 | |
| | 2.02 | | 1.79 | |
| | 2.11 | | 1.86 | |
| | 2.14 | 2.062 | 1.85 | 1.842 |

TANNINS.

We have already pointed out that Ma Huang means astringent yellow, and that the "Ma" or "astringent" refers to the taste of the drug. The literature repeatedly emphasizes the astringent taste and many references state that this is due to the presence of a tannin.

The astringent taste is also perceptible in several of the American species of Ephedra, and it has been suggested that in the case of Ephedra nevadensis, the remedial action of the drug is probably due to a tannin (20).

Although tannin has generally been accepted as one of the constituents of Ma Huang, yet we find little information in literature regarding this constituent of the drug. We have, therefore, undertaken the problem of determining the kind and amount of tannin present in our samples.

Generic tests on the aqueous extract of the drug indicated the possibility of a tannin being present. The following tests were given:

| Reagent. | Result. |
|---|---|
| Ferric chloride solution | Greenish black color |
| Gelatin solution | Precipitate |
| Copper acetate | Precipitate |
| Lead acetate | Precipitate |
| Potassium dichromate | Negative |
| Methylene blue | Precipitate |
| Ammonium hydroxide | Solution readily absorbs oxygen and darkens |
| Potassium ferricyanide and Ammonium hydroxide | Red-orange color |
| Fehling's solution | Reduction takes place |
| Basic lead acetate | Precipitate |
| Ammonium molybdate in concentrated Ammonium chloride | Yellow precipitate |
| Lime water | White precipitate |
| Iodine potassium iodide with Ammonium hydroxide | Green precipitate |
| Bromine water | Yellow precipitate |

These tests seem to give quite conclusive evidence of the presence of a tannin. Our next step was an attempt to classify the tannin. We concluded that the tannin in Ma Huang belonged to the catechol group because it conformed to the following tests:

| Reagent. | Result. |
|---|---|
| Iron alum | Greenish black color |
| Bromine water | Yellow precipitate |
| Concentrated sulphuric acid | A red ring forms at the point of junction |
| When boiled with acids | Deposits red coloring matter |

The tests for pyrogallol tannins were negative. However, in order to prove still more conclusively that Ma Huang tannin was a member of the catechol group, we ran the following test: 50 cc. of the tannin solution were boiled for half an hour under a reflux condenser with 25 cc. of a mixture of 100 cc. of concentrated hydrochloric acid (diluted with an equal volume of water) and mixed with 150 cc. of 40% formaldehyde; 10 cc. of the filtrate from the above, mixed with 10 drops of 1% iron alum and 1 Gm. of solid sodium acetate gave no color.

We attempted to limit our tannin still further by running the different tests for the various tannins of the catechol group. The fact that our tannin was precipitated from its solution by the addition of lead acetate, immediately excluded the possibilities of either resorcinol or hydroquinone being present. Our tests for catechol and protocatechuic acid gave the following results:

| Reagent. | Result. |
|---|---|
| Lead acetate | Precipitate (both) |
| Silver nitrate | Reduction takes place (catechol) |
| Fehling's solution | Reduction takes place (catechol) |
| Ferrous salts | Violet color (protocatechuic acid) |
| Ferric chloride plus sodium carbonate | Green color darkening upon addition of sodium carbonate |
| Ferric chloride plus sodium acetate | Green color darkening upon addition of sodium acetate |

These results seem to indicate the possibility of either catechol or protocatechuic acid being present.

Since many tannins are substances of a glucosidal nature and occur in the plant in combination with a carbohydrate complex such as glucose, we endeavored to determine whether or not the tannin of Ma Huang was of this nature. We extracted the tannin from the crude drug by agitating the aqueous extract of the drug with ether and then saturating the aqueous solution with common salt and shaking with ethyl acetate. The ethyl acetate was evaporated and a yellowish brown, fluffy looking powder was obtained. Although this material looked much like a tannin, it did not conform to the usual tannin tests.

This material extracted with ethyl acetate was boiled under a reflux condenser with HCl (2%) for an hour. Upon cooling, a red amorphous powder separated out. If our original substance was a tannin, this red powder was probably a phlobaphene. After filtering the mixture, the filtrate was shaken with ether and the aqueous solution was boiled, neutralized with caustic soda and precipitated with basic

lead acetate. The solution was again filtered and any lead remaining in solution was removed by the addition of dilute sulphuric acid. The solution was once more filtered and the clear filtrate was heated to boiling with Fehling's solution but no reduction took place. This would seem to indicate that the tannin present in Ma Huang is not in glucosidal combination.

Our attempts to determine the amount of tannin present were not particularly successful. We were not able to obtain concordant results with different methods of analysis nor were our results with the same methods always consistent. All of our results, however, would indicate that the tannin content is above 10%.

SAPONINS.

Generic tests indicated that a saponin-like body was present in Ma Huang. We also noted that after extracting the drug with benzene, ether, chloroform and alcohol, the water extract foamed strongly upon heating. Some trouble with emulsions was also experienced with some of the assay processes. We attempted the separation of this constituent by extracting the crude drug with hot alcohol and subsequent precipitation with ether. We obtained a fluffy, flocculent, white precipitate which readily darkened and resinified after it had been filtered.

We carried out this isolation process again, this time purifying the saponin by dissolving it in water and treating it with lead acetate. The resulting lead salts were decomposed by treating with dilute sulphuric acid.

The purified saponins thus obtained, were found to conform to the following tests for saponins:

1. Aqueous extracts foamed readily when shaken.
2. Concentrated sulphuric acid produced a red color.
3. Concentrated sulphuric acid containing a little ferric chloride gave a bluish green color.
4. Upon hydrolysis, the substance yielded a reducing sugar.

Therefore we have isolated and definitely established the presence of a saponin as one of the constituents of Ma Huang.

GLUCOSIDES.

Some of our generic tests seemed to indicate the possibility of a glucoside being present, however, we could not be sure that these tests were due to strictly glucosides and not to glucosidal substances such as certain tannins, pigments or saponins.

In order to isolate any glucosides that might be present in the drug, we extracted the material with dilute alcohol and precipitated other materials by adding a solution of lead acetate. The lead was removed from the solution by treating it with hydrogen sulphide. The aqueous solution was evaporated and the residue was taken up with dilute alcohol. A few crystals separated out. Their solution was very bitter and did not reduce Fehling's solution until after the material had been hydrolyzed by treating with acid and refluxing for a period of ten hours. This crystalline material did not have a sharp melting point as it charred. The charring did not take place until the material had been heated to almost 200° C. A few crystals were fused with sodium and tested for the presence of nitrogen but no positive test was obtained.

From our experiments we concluded that a glucoside or a glucoside-like body was present as one of the constituents of Ma Huang.

SUMMARY AND CONCLUSIONS.

1. A proximate analysis of Ma Huang has been made.

2. A study of the assay methods of Ma Huang shows that there is much variation in the results obtained by using the different methods.

3. A new method of assay using barium hydroxide for liberating the alkaloids from the plant tissue has been developed and is recommended for the determination and isolation of the alkaloids.

4. Good species of Ma Huang should yield close to 2% total alkaloids.

5. A catechol tannin has been found to be present as one of the constituents of Ma Huang. This tannin may be catechol, protocatechuic acid or both.

6. A crystalline substance possessing glucosidal properties has been isolated.

7. A saponin has been isolated and determined as one of the constituents of Ma Huang.

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# THE ASSAY OF PREPARATIONS CONTAINING PEPSIN OFFICIAL IN THE NATIONAL FORMULARY.*,[1]

BY GLENN L. JENKINS AND EDWARD M. HOSHALL.

INTRODUCTION.

The medicinal value of pharmaceutical preparations containing pepsin is commonly considered to be dependent upon the activity of this enzyme in the digestion of proteins. The present official method of assay of pepsin (1) based on the digestion of egg albumen has been shown to yield erroneous results due to numerous variable factors (2), (3). Methods have not been developed for the assay of preparations containing pepsin, consequently the only criterion of the quality of a

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[1] Scientific Section, A. PH. A., Toronto meeting, 1932.

preparation containing pepsin is that based on the activity of the pepsin employed in the compounding.

The results of a prescription survey by Gathercoal (4) indicate that the National Formulary preparations containing pepsin are extensively prescribed in modern pharmacy. It is considered highly desirable, therefore, to develop methods for the assay of these preparations with the intent that a satisfactory method might be made official in the next edition of the National Formulary. A positive result in this study would make possible the preparation of standardized preparations containing pepsin, and it would also make possible studies of methods for the stabilization of these preparations.

## METHODS OF ASSAY.

Numerous methods have been proposed for the estimation of the proteolytic activity of pepsin. These methods may be grouped into three main classes, namely:

1. Methods based on determination of unaltered substrate.
2. Physical methods based on determination of cleavage products.
3. Chemical methods based on determination of cleavage products.

To the first group belong the methods of Ebstein and Grutzner (5), Mett (6), Volhard (7), Gross (8), Rona and Keinmann (9), Fuld and Levison (10), Rose (11), Jacoby-Selms (12) and Waldschmidt (13). This class contains the methods of historical significance; and while they permit relative measurements, they are not of sufficient accuracy to consider for this work.

The second group comprises the work of Fermi (14), Palitzsch and Walbum (15), Henri and Bancels (16), Abderhalden and Koelker (17), and Allen (18), Northrop (19) and Spriggs (20). With the exception of the method of Abderhalden and Koelker which is only applicable for use with optically active peptides, the others are too restricted in their applicability and not suited for a general method.

The remaining group contains the methods of Van Slyke (21), Sörensen (22), Willstätter and Waldschmidt-Leitz (23), Volhard (24), Foreman (25) and Jenkins and Greenberg (26). The methods were all reviewed but since that of Greenberg is by far the simplest and appears to be the most generally applicable, it was selected for a study of the determination of pepsin in National Formulary preparations.

## EXPERIMENTAL PART.

In order to obtain a working knowledge of the method, four samples of commercial pepsin were obtained. Pepsin A had been repeatedly assayed by the U. S. P. X method and its proteolytic activity was determined to be 92 per cent. Pepsin B was assayed by the A. O. A. C. method (27), and using Pepsin A as standard, a proteolytic activity of 115 per cent was found for Pepsin B. Pepsin C and Pepsin D were unassayed, samples each from a different manufacturer.

The following pepsin containing preparations of the National Formulary 5th Edition (1926) were compounded: **Elixir Pepsini, Elixir Pepsini Bismuthi Et Strychninæ, Elixir Pepsini Compositum, Elixir Pepsini Et Bismuthi, Elixir Pepsini Et Rennini Compositum, Liquor Pepsini, Liquor Pepsini Antisepticus, Liquor Pepsini Aromaticus, Glyceritum Pepsini, Pepsinium Saccharatum.**

The methods used in their preparation were essentially the same as specified in the National Formulary, except that all weighings were made on the analytical balance, volumes were made at 20° C. in volumetric apparatus, and little or no agitation was used to effect solution of the pepsin. The solutions were carefully filtered (covered to prevent evaporation) into four-

ounce, narrow-mouth, amber bottles, stoppered and sealed with wax, and kept at 15° C. except when a sample was withdrawn. In all cases, the maximum amount of pepsin specified by the National Formulary was used. The pepsin used in all the preparations was Pepsin A.

The method of Greenberg was followed with one modification, namely, 20 cc. of 0.1*N* NaOH was added instead of 100 cc. of 0.02*N* NaOH; this reduced the total volume and made the titration more accurate. The method as modified was:

"Pipette 25 cc. of the casein solution into a 350-cc. Erlenmeyer flask. Stopper the flask and warm to 40° C. in a constant temperature bath. Add 25 cc. of the pepsin solution, stopper, invert the flask once and allow to digest at 40° C. in the constant temperature bath for 15 minutes. Remove the flask from the bath, add 25 cc. of the formaldehyde solution and rotate the contents of the flask for 2 minutes. Add 20 cc. of 0.1*N* NaOH, mix well and titrate the excess of alkali with 0.02*N* HCl. Conduct a blank test in the same manner. Subtract the number of cc. of 0.02*N* HCl consumed in the actual test from the number of cc. used in the blank. The difference represents the number of cc. of 0.02*N* alkali required to neutralize the acidity developed during proteolytic digestion. Divide the result by 3 and multiply by 100 to obtain the percentage strength of the pepsin; the figure 3 is equivalent in terms of 0.02*N* alkali of pepsin of 100 per cent activity. Since each 0.1 cc. of difference in the amount of alkali found in the blank test corresponds to 3.33 per cent of proteolytic activity, all volumetric measurements must be made with considerable accuracy."

Using the modified method, six duplicate determinations were made on Pepsin A and Pepsin B, with the following results:

TABLE I.—PROTEOLYTIC ACTIVITY.

| Pepsin A. | | Pepsin B. | |
|---|---|---|---|
| 1. | 2. | 1. | 2. |
| 97.3 | 100.0 | 96.7 | 98.3 |
| 100.3 | 108.0 | 106.3 | 109.3 |
| 100.0 | 101.7 | 103.3 | 108.3 |
| 105.0 | ... | 108.5 | 109.7 |
| 98.3 | 103.3 | | |
| 102 | Average | 105 | |

The checks on duplicate determinations are within experimental error, but a 12 per cent maximum deviation on determinations leaves much to be desired. The proteolytic activity of the pepsin samples as determined by the U. S. P. X method check the proteolytic activity as here determined by 10 per cent.

The method of assay was applied to the following pepsin preparations as tabulated below. In each case the preparations were taken from storage at 15° C. and when at 20° C. a volume was removed, such that when diluted, 25 cc. of the solution contained 0.025 Gm. of Pepsin A. The proteolytic activity was calculated the same as in the original method, namely, that the number of cc. difference of 0.02*N* HCl between the sample and the blank determination, was multiplied by 33.33, which expressed the proteolytic activity in per cent. The following results were obtained:

TABLE II.

| Preparation. | Proteolytic Activity in Per Cent. 1. | 2. | 3. | 4. | Ave. |
|---|---|---|---|---|---|
| Glyceritum Pepsini | 47.6 | 56.6 | 50.3 | 54.3 | 52.2 |
| Pepsinum Saccharatum | 105.3 | 104.7 | 101.0 | 102.7 | 103.4 |
| Elixir Pepsini | 67.3 | 66.3 | ... | ... | 66.8 |
| Liquor Pepsini Aromaticus | 68.0 | 69.0 | ... | ... | 68.5 |
| Liquor Pepsini Antisepticus | 67.7 | 67.0 | ... | ... | 67.4 |
| Liquor Pepsini | 100.3 | 103.0 | ... | ... | 101.7 |
| Liquor Pepsini Et Bismuthi | 142.7 | ... | ... | ... | 142.7 |
| Liquor Pepsini Et Strychninæ | 139.7 | 147.7 | ... | ... | 143.7 |

The result of this series of determinations shows that except in the case of **Pepsinum Saccharatum** and **Liquor Pepsini** the method is not applicable to the assay of these preparations.

Thus only in two cases out of eight does the amount of pepsin added compare favorable with that found. The other six samples vary from 40 per cent to 152 per cent. The causes for these variations were considered to be as follows:

1. With one exception (**Pepsinum Saccharatum**), diluted hydrochloric acid is used in making up the preparations, and the acidity of the sample is not accounted for in the assay. For example, it can be calculated that for Elixir Pepsini this error would be equivalent to a proteolytic activity of 16 per cent. In other preparations the error would be still greater.
2. Essential oils and other flavoring materials are employed to make the preparations. If there were a reaction of these materials with any reagents used, due to the fact that no blank is run on the sample, this would be unaccounted for.
3. There may be a reaction between the formaldehyde and the pepsin.
4. The $p_H$ of the digestion mixture may be a factor. Although the $p_H$ of the substrate, casein, is prepared at $p_H$ 1.4, the added pepsin containing solutions of various acidities will change this $p_H$.
5. The difficultly determined end-point.

It was then decided to temporarily discontinue work on National Formulary preparations and using samples of commercial pepsins, to evolve a method where variations due to the "reagent blank" might be accounted for, and to subject the method to further study in the light of the following factors:

1. The acidity of the aqueous solution of pepsin,
2. The reaction between pepsin and formaldehyde,
3. The effect of $p_H$ on degree of proteolytic activity, and
4. The difficultly determined end-point.

*1. Acidity of the Aqueous Solution of Pepsin.*—The four commercial samples of "U. S. P. Quality" Pepsin as previously described, were used as representative. Solutions of 0.25 per cent were prepared in pure distilled water and a 10-cc. aliquot titrated with 0.02*N* NaOH, using two drops of 1 per cent phenolphthalein in neutral alcohol as indicator, to a faint pink.

TABLE III.

| Pepsin. | Concentration. | No. Cc. | Cc. 0.02*N* NaOH. | |
|---|---|---|---|---|
| A | 0.25 | 10.0 | 1.20 | 1.25 |
| B | 0.25 | 10.0 | 0.47 | 0.46 |
| C | 0.25 | 10.0 | 2.75 | 2.80 |
| D | 0.25 | 10.0 | 0.90 | 0.85 |

On the basis of the factor used in the Greenberg assay, namely, 3.00 cc. of 0.02*N* acid equivalent to 100 per cent proteolytic activity, the results here indicate that due to the acidity of the sample an apparent proteolytic activity ranging from 15 per cent to 93 per cent could be obtained. No account of this factor was taken in the original assay, obviously it must be accounted for, either by another titration or by its inclusion in the "reagent blank."

*2. The Reaction between Pepsin and Formaldehyde.*—Three commercial samples of pepsin (Pepsin A, C and D) were used. A 0.25 per cent solution, in pure distilled water of each sample, was prepared and a 10-cc. aliquot was titrated with 0.02*N* NaOH, using phenolphthalein (1 per cent in neutral alcohol), to a faint pink color. To this was added 10 cc. of a 40 per cent solution of "Reagent Quality" formaldehyde, which had been previously rendered neutral with sodium hydroxide, using phenolphthalein as indicator. Upon the addition of the formaldehyde the solution became acid: the acidity then being determined by titration with 0.02*N* NaOH, using phenolphthalein, to a faint pink color.

TABLE IV.

| Pepsin. | Concentration Per Cent. | No. Cc. Pepsin (Neutral). | No. Cc. Formaldehyde (Neutral). | No. Cc. 0.02*N* NaOH (to Neutralize). | |
|---|---|---|---|---|---|
| A | 0.25 | 10.0 | 10.0 | 1.81 | 1.80 |
| C | 0.25 | 10.0 | 10.0 | 2.65 | 2.60 |
| D | 0.25 | 10.0 | 10.0 | 2.20 | 2.24 |

Table IV shows that there is a definite reaction between the pepsin in aqueous solution and the formaldehyde.

To determine if this reaction was proportional to the amount of pepsin present, varying amounts of pepsin were treated with neutral formaldehyde.

TABLE V.

| Pepsin. | Concentration Per Cent. | No. Cc. Pepsin (Neutral). | No. Cc. Formaldehyde (Neutral). | No. Cc. 0.02*N* NaOH (to Neutralize). |
|---|---|---|---|---|
| A | 0.25 | 10.0 | 10.0 | 1.80 |
| A | 0.25 | 20.0 | 10.0 | 3.55 |
| A | 0.25 | 30.00 | 10.00 | 5.67 |
| A | 0.25 | 40.00 | 10.0 | 7.32 |

Table V indicates that the reaction is directly proportional to the amount of pepsin present.

The amount of pepsin was then held constant and the amount of formaldehyde varied, with the following results:

TABLE VI.

| Pepsin. | Concentration Per Cent. | No. Cc. Pepsin (Neutral). | No. Cc. Formaldehyde (Neutral). | No. Cc. 0.02*N* NaOH (to Neutralize). |
|---|---|---|---|---|
| C | 0.25 | 10.0 | 1.0 | 2.15 |
| C | 0.25 | 10.0 | 2.0 | 2.35 |
| C | 0.25 | 10.0 | 5.0 | 2.55 |
| C | 0.25 | 10.0 | 10.0 | 2.65 |
| C | 0.25 | 10.0 | 20.0 | 2.64 |

It appears from Table VI, that, within limits, the amount of formaldehyde is not a factor in this reaction.

A definite reaction, therefore, proportional to the amount of pepsin present, takes place when formaldehyde is added to aqueous solutions of pepsin. The blank accordingly, of the Greenberg Assay, should take care of this reaction or else a separate titration and correction should be applied to the existent method. In view of the lack of positive knowledge concerning the structure of pepsin, Hammarsten (28), the cause of this reaction can only be conjectured, Sherman (29) and Johannessohn (30) indicate that formaldehyde in concentrations from 5 to 10 per cent does not inhibit the proteolytic activity of pepsin.

*3. The Effect of Hydrogen-Ion Concentration on the Proteolytic Activity of Pepsin.*—The lack of a satisfactory quantitative method precludes experimental work, but a survey of the literature relative to the proteolytic action of the enzyme pepsin on casein, notably the work of Northrop (31) and Grant (32), indicates that the optimum proteolytic activity is approximately at $p_H$ 1.8 to $p_H$ 2.0. In the following experimental work this acidity is maintained within those limits, rather than at $p_H$ 1.4 as was the case in the Greenberg Assay.

*4. The Difficultly Determined End-Point.*—The determination of the end-point is effected by titration of the digestion mixture, the formaldehyde and the excess alkali (a total volume of some 200 cc.) with 0.02*N* acid. A check to within 0.30 cc. (5 drops) is difficult, save only to the analyst who has performed the titration many times. Jodidi (33) comments upon the unsatisfactory end-point in a like titration. It was found by experiment that slight modifications in the procedure gave a better end-point, namely: 1. It is possible to use 20 cc. of 0.1*N* NaOH in place of 100 cc. of 0.02 NaOH, with a decrease of volume and an increase of accuracy. 2. The pepsin solution may be made more concentrated, 10 cc. of a 0.25 per cent solution being used instead of 25 cc. of a 0.10 per cent solution. 3. The amount of formaldehyde was reduced from 25 cc. to 15 cc. as the latter amount was found to be sufficient. 4. By the use of a blue light to titrate, the red tinge due to the phenolphthalein could be more closely followed, and more accurate results obtained.

## DISCUSSION OF RESULTS.

The application of the Sörenson formal titration method as modified by Greenberg, to the assay of pepsin containing preparations official in the National Formulary, was unsuccessful. The method was considered unsuited for the following reasons:

1. In an effort to find the source of difficulty, commercial samples of pure pepsin were assayed by the Greenberg Method. The results for two samples were in fair agreement with those obtained by Mr. Greenberg, but when other samples were analyzed by the same method, serious discrepancies were observed, and it was indicated that the results obtained were not in proportion to the proteolytic activity.

2. Several samples of pepsin tested showed definite and different acidities in aqueous solution. Because of the fact that a blank was not run on the pepsin solution, this initial acidity was entirely unaccounted for. Thus a pepsin with a high acidity would assay a high proteolytic activity.

3. For all samples of pepsin examined, there was a definite reaction with formaldehyde and different amounts of acid were liberated, which affected the results of the assay.

4. The consensus of recent work with the enzymic action of pepsin on casein indicate that $p_H$ 2.0 is the optimum hydrogen-ion concentration rather than $p_H$ 1.4 as used.

5. The determination of the end-point in the method was difficult, and the modifications suggested and used, although rendering the titration more accurate still leave much to be desired.

6. The formaldehyde was a source of apparent error, commercial samples being difficult to neutralize, turning brown and quickly developing acidity on exposure to air.

7. Another point is suggested when we find the ratio of pepsin to casein as 1:1, while pepsin will digest 3000 times its weight of egg albumen.

### FOREMAN'S METHOD.

Foreman (25) proposed a method for the assay of pepsin based on the proteolytic splitting of protein and titration of the liberated carboxy groups in 80 to 90 per cent ethyl alcohol solution, where the free amino groups form no compounds with the phenolphthalein used as indicator, and consequently the acid alone can be titrated with standard alkali in alcoholic solution. The improvements on the orignal method by Willstätter and Waldschmidt-Leitz (23) indicate a method that is generally applicable for most proteolytic degradation products. The method was slightly modified, and the following procedure was adopted in order to determine the proteolytic activity of samples of pepsin previously assayed by the U. S. P. X method.

Reagents:

1. A 0.25 per cent solution of pepsin, freshly prepared, in pure distilled water.
2. Casein solution, prepared as follows: to 45 cc. of 0.5*N* HCl in a 250-cc. volumetric flask, add 5 Gm. of Hammarsten's Casein (Merck), and 150 cc. of distilled water. Heat on a water-bath until a clear solution is obtained. Remove, cool and fill to mark. Add 5 cc. of xylene as preservative.
3. Phenolphthalein indicator solution. A 1 per cent solution of phenolphthalein in neutral alcohol.
4. Alcoholic 0.02*N* HCl.
5. Alcoholic 0.1*N* NaOH.

Procedure:

Measure 10 cc. of the casein solution into a 250-cc. Erlenmeyer flask, warm to 40° C. then add 10 cc. of the pepsin solution, shake with a swirling motion and allow to remain in the bath 20 minutes. Remove, cool to room temperature, add 100 cc. of ethyl alcohol, 10 cc. of 0.1*N* NaOH and 2 cc. of indicator solution. Titrate to the disappearance of the pink color.

The blank is determined as follows: To 10 cc. of the casein solution add 100-cc. of alcohol, 10 cc. of 0.1 alcoholic NaOH, 10 cc. of pepsin solution and 2 cc. of indicator. Titrate to the same end-point as above.

The difference in the number of cc. of 0.02*N* alcoholic HCl required between the blank and the sample, indicate the apparent proteolytic activity.

Several determinations were carried out by this method. The temperature was maintained at 40° ± 2° C. The casein solution as prepared was of $p_H$ 1.8 and when the sample was added the $p_H$ was 1.85 to 1.90. The time of digestion was 20 minutes. For the same sample of pepsin (Pepsin A), the following results were obtained, expressed in cc. of 0.02*N* alcoholic HCl difference between the blank titration and the titration of the digested protein.

TABLE VII.

| No. of Run. | Cc. 0.02*N* HCl (Difference). | Cc. 0.02*N* HCl (Difference). | Casein Solution. |
|---|---|---|---|
| 1 | 4.06 | 4.18 | A 2.0 Gm./100 cc. |
| 2 | 0.32 | 0.40 | B 2.0 Gm./100 cc. |
| 3 | 4.26 | 3.80 | C 2.0 Gm./100 cc. |
| 4 | 3.60 | 3.96 | C 2.0 Gm./100 cc. |
| 4 | 3.95 | 3.78 | C 2.0 Gm./100 cc. |
| Average | 3.95 | | |

With the exception of Run No. 2, the results were fairly reproducible. The checks on duplicate determinations are poor and the maximum deviation from the average is about 9 per cent.

To test the applicability of the method to National Formulary pepsin containing preparations, samples of Elixir Pepsini, Pepsinium Saccharatum and Glycertium Pepsini (see page No. 3), were removed from storage (they were four months old), and a quantity diluted so that 10 cc. contained the equivalent of 0.025 Gm. of Pepsin A, the same amount of pepsin as used in the above runs. The results are as follows:

TABLE VIII.

| Preparation. | Cc. 0.02*N* HCl (Difference). | Cc. 0.02*N* HCl (Difference). | Casein Solution. |
|---|---|---|---|
| Pepsinium Saccharatum | 3.68 | 3.78 | D 2.0 Gm./100 cc. |
| Elixir Pepsinium | 3.46 | .. | D 2.0 Gm./100 cc. |
| Glyceritum Pepsinium | 3.42 | 3.33 | D 2.0 Gm./100 cc. |

The acidity developed for the above preparations compared with like amounts of Pepsin A is lower, as would be expected due to decrease of proteolytic activity resulting from agitation in preparation and storage. The question then arises as to whether the acidity developed is directly proportional to the amount of pepsin present. Varying amounts of pepsin were then used to digest the casein, following the same method as before.

TABLE IX.

| Sample. | | Cc. 0.02*N* HCl (Difference). | Cc. 0.02*N* HCl (Difference). | Casein. |
|---|---|---|---|---|
| 10 cc. (heated to 100) | | 0.21 | .. | 2.0 Gm./100 cc. |
| 5 cc. | 0.0125 Gm. | 2.75 | 2.45 | (New lot which |
| 10 cc. | 0.0250 Gm. | 3.10 | 3.06 | dissolved with |
| 15 cc. | 0.0375 Gm. | 4.39 | | difficulty.) |
| 20 cc. | 0.0500 Gm. | 4.78 | | |

By inspection of the above results it is seen that when the concentration of the pepsin is varied the acidity developed is not directly proportional to the amount of enzyme present. A partial explanation is that the substrate, casein, must be increased if proportional results are to be obtained. Furthermore, according to Volhard and Löhlein (34) casein combines with a definite amount of HCl, and if the casein is digested by the enzyme, the combined acid is liberated. Thus in any case of casein digestion by pepsin, there will be two sources of acidity developed. 1. Acidity due to the proteolytic splitting of the protein which is titratable if the amino groups are "blocked off" with either formaldehyde, acetone or alcohol. 2. Acidity developed by digestion of the casein combined with HCl, with the subsequent liberation of the HCl.

The method was considered unsuitable, for the following reasons:

1. A 2 per cent solution of casein is difficult to prepare and to preserve. Different lots of Hammarsten's Casein (Merck) were found to have different solubilities. Regarding the preservation, Treyer (35) and Price (36) show that chloroform injures all enzymes to a varying extent, and they further find that ether and alcohol have very little effect while toluol has even less effect on enzymes. Toluol was first used, then xylene was tried, and found to be appreciably better as a preservative.

2. Titration with 0.02*N* alcoholic HCl in a volume of 125 cc. using phenolphthalein, is difficult, and checks within 0.30 cc. are unusual, and obtained only with practice.

3. The acidity developed is not in direct proportion to the amount of pepsin present.

4. Results with identical solutions of casein were not reproducible within 10 per cent, and even greater variations were found with the use of different batches of casein.

5. The titrated acidity in any of the methods whereby the amino group is blocked off, is not due to the presence of the remaining acid group alone, but also another factor: the breakdown of an addition product of casein with HCl, which liberates HCl that is titrated along with the proteolytically developed acidity.

6. This method was discarded.

### ACETONE TITRATION METHOD.

Although it has been indicated that in any method where casein is digested, and the amino groups "blocked off," the results are not directly proportional to the amount of pepsin present, and are of doubtful value, it was decided to investigate the method recommended by Waldschmidt (37). According to K. Linderström-Lang (38) the proteolytic mixture is titrated with 0.1*N* HCl in alcoholic solution, after adding acetone from 85–95 per cent concentration. This method will effectively block off most amino groups. With some slight modifications the method was essentially the same as that of Forman. The procedure is as follows:

Add 10 cc. of the casein solution to a 250-cc. Erlenmeyer flask, heat to 40° C. and then add 10 cc. of pepsin solution shaking with a swirling motion; allow to remain on bath 20 minutes, remove, cool to room temperature and add 100 cc. of acetone, 10 cc. of 0.1*N* alcoholic NaOH and 2 cc. of indicator solution. Titrate with 0.02*N* alcoholic HCl to a faint pink.

The blank is determined as follows: To 10 cc. of the casein solution add 100 cc. of acetone, 10 cc. of 0.01*N* alcoholic NaOH, 10 cc. of the pepsin solution and 2 cc. of the indicator solution. Titrate to the same end-point as above.

The difference in the number of cc. of 0.02*N* alcoholic HCl required, is a measure of the apparent proteolytic activity.

Three determinations were made by the above method, and then the concentration of the pepsin was varied. The results are given:

TABLE X.

| Sample (Pepsin A). | Cc. 0.02*N* HCl (Difference). | Casein. |
|---|---|---|
| 10 cc. | 3.41 | 2.0 Gm./100 cc. (casein was difficultly soluble) |
| 10 cc. | 3.90 | |
| 10 cc. | 3.60 | |
| 5 cc. | 2.76 | |
| 10 cc. | 3.60 | |
| 15 cc. | 4.39 | |
| 20 cc. | 4.78 | |

The results show that close checks on identical samples were not obtained, and that the developed acidity was not directly proportional to the pepsin present. The end-point of the titration was much more accurate than when the alcohol was used to "block-off" the amino groups. The casein itself is a source of trouble, since it is difficultly soluble, does not form a clear solution and ultimately settles out. To offset this, the use of solid casein instead of the solution was next investigated. The method was the same except that 0.5 Gm. of Hammarsten's Casein (Merck) was used, and 10 cc. of 0.1*N* HCl added, giving a $p_H$ of 1.9.

TABLE XI.

| Sample. | | Cc. 0.02*N* HCl (Difference). | Casein. |
|---|---|---|---|
| 10 cc. (heated to 100) | | 0.10 | 0.5 Gm., (Hammarsten's) |
| 2 cc. | 0.010 Gm. | 10.11 | |
| 5 cc. | 0.025 Gm. | 13.54 | |
| 10 cc. | 0.050 Gm. | 13.71 | |
| 20 cc. | 0.100 Gm. | 14.80 | |

Under the new conditions, increasing both the concentration of pepsin and casein, it was found that increased acidity was the result. As before, the acidity is not satisfactorily proportional to the amount of pepsin. The increase in the developed acidity may be explained by increased enzyme concentration and also increased casein, the latter contributing acidity from the breakdown of its HCl addition product, as previously explained. The following conclusions are given for this method:

1. Acetone is more satisfactory as a "blocking-off" medium than alcohol, since the former allows of a more accurately determined end-point.
2. The acidity developed is not in direct proportion to the amount of pepsin present.
3. The use of solid casein is recommened for digestion, and in greater concentrations than hitherto used.
4. The method has possibilities as an empirical method, but an accuracy within 10 per cent would be difficult to obtain.
5. This method was discarded.

### VOLHARD'S METHOD.

Volhard and Löhlein (34) suggest a method based upon the fact that casein combined with a definite amount of HCl, and if the casein has been digested by the enzyme, the combined HCl is liberated. The increase in the amount of free HCl compared with that of the original solution, as determined by titration, serves as a measure of enzyme activity. The acidity of the pepsin solution is determined and added to that of the original solution. The method is as follows:

"A 5 per cent casein solution is prepared by suspending the casein in a small amount of water, dissolving in NaOH solution (8 cc. of *N* NaOH per 10 Gm. of casein), making up to volume with water and warming to 90° C. Then 150 cc. of 0.7*N* HCl and 100 cc. of the casein solution are mixed, the mixture is warmed to 40° C. and the proper amount of pepsin solution is added, and the mixture is diluted to 300 cc. with water warmed to 40° C. At the end of the incubation period (24 hours usually), 100 cc. of 20 per cent sodium sulphate is added, thus precipitating the undigested casein. The solution is filtered and 100 cc. of the filtrate is titrated with 0.1*N* NaOH using phenolphthalein as indicator. The difference between the titration value of the digest and that of the original solution, and of the pepsin solution indicates the increase in acidity of the digest. When the increase in acidity is denoted by $v$, and the time of digestion in hours by $t$, the quantity of enzyme used by $f$, and $x$ the actual pepsin concentration, then according to the Schütz-Borrissov Equation (39),

$$x = (f \times t)^2/v^2$$

A consideration of the above method from a practical standpoint will show that it is too involved and lengthy to be readily applicable. Some points of criticism are as follows:

1. A third titration is necessary to account for the acidity of the pepsin solution. 2. The casein solution is difficult to prepare and to preserve. 3. The acidity of a solution prepared as above, and after the pepsin had been added was found to be $p_H$ 2.4 which is well above the optimum $p_H$ for casein digestion by pepsin. 4. The time, 24 hours, must be reduced, if a practical rapid method is desired. 5. The volumes are too large, making for bulky apparatus, and requiring a large working space.

A tentative method was devised as follows:

Reagents:

Casein "Technical Grade."

Pepsin Solution (freshly made 0.1% in distilled water), or a preparation adjusted by dilution to contain 0.010 Gm. of pepsin in 10 cc.

Sodium sulphate, 20% on distilled water.

Phenolphthalein Indicator, 1% in neutral alcohol.

0.1*N* Hydrochloric acid.

0.5*N* Hydrochloric acid.

0.5*N* Sodium hydroxide.

Method:

Into a 250-cc. Erlenmeyer flask introduce 3 Gm. of powdered casein, 50 cc. of distilled water and 10 cc. of 0.5*N* hydrochloric acid. Heat the flask to 90° C.

on the water-bath and then cool to 40° C. Then add the sample of pepsin and sufficient water from a burette to make the total volume 80 cc. Maintain the mixture at 40° C. exactly thirty minutes, with occasional shaking. The flask should be lightly stoppered. Remove from the bath, add exactly 20 cc. of the sodium sulphate solution, shake by swirling and filter using a folded filter. To 50 cc. of the filtrate (one-half the original volume), add from a burette sufficient 0.5*N* sodium hydroxide to have about 2 cc. excess and back titrate the alkali with 0.1*N* hydrochloric acid using phenolphthalein indicator. Titrate rapidly to the first colorless end-point.

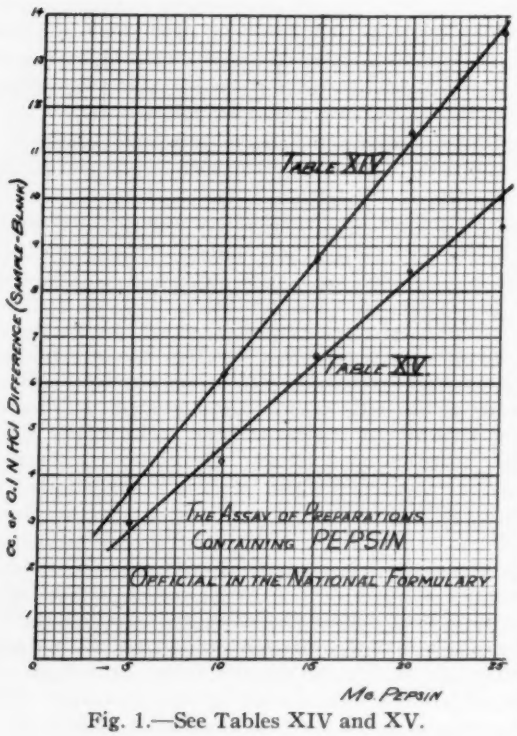


Fig. 1.—See Tables XIV and XV.

A blank is run simultaneously as follows: Into a 250-cc. Erlenmeyer flask introduce 3 Gm. of casein, 50 cc. of distilled water and 10 cc. of 0.5*N* hydrochloric acid. Stopper lightly, heat to 90° C. on a water-bath and cool to 40° C., then add sufficient water from a burette to make the total volume 80 cc. Maintain the mixture at a temperature of 40° C. for thirty minutes. Remove from the bath and add 20 cc. of sodium sulphate solution, shake by swirling and filter. To 50 cc. of the filtrate (one-half the original volume), add about 2 cc. excess of 0.5*N* sodium hydroxide, and one-half the volume of pepsin solution used in the determination. (This is necessary in order to correct for the acidity of the pepsin solution.) Back titrate with 0.1*N* hydrochloric acid to the same end-point as in the determination.

Calculation: The difference between the titration of the sample determination and the blank determination expressed in cc. of 0.1*N* hydrochloric acid may be taken as an expression of the relative proteolytic activity of the product being assayed.

The standard is calculated from a series of determinations using pepsin of known proteolytic activity (standardized by U. S. P. X Method), and plotting a graph showing the relationship between the amount of pepsin used and the cc. of 0.1*N* hydrochloric acid difference in titration between the blank and the sample.

Example: Standard will be Pepsin X, with a proteolytic activity of 100% (U. S. P. X). By the above method:

| | | |
|---|---|---|
| 0.005 | | 3.68 |
| 0.010 | Gm. pepsin | 6.20 cc. 0.1*N* HCl (difference in titration) |
| 0.015 | | 8.74 |

Sample made into solution of 0.01 Gm. of pepsin (based on declaration) per 10 cc. By above method 0.010 Gm. gave a difference in titration of 5.84 cc.

By interpolation we find that the sample will have a proteolytic activity of 93%.

$$\frac{6.20}{3.68} \quad \frac{5.84}{3.68} \quad \frac{2.16}{2.52} \times (0.010-0.005) = 0.00428$$

$$0.005 + 0.00428 = 0.00928 \text{ Gm.} \quad \text{Standard} = 0.010 \text{ Gm.} \frac{0.00928}{0.010} \times 100 = 92.8\%$$

Using varying amounts of Pepsin A, determinations were made by the above method with the following results:

TABLE XII.

| Sample of Pepsin. | | Cc. 0.1*N* HCl (Difference). | Comments. |
|---|---|---|---|
| 2 cc. | 0.002 Gm. | 3.40 | Casein 5 Gm. |
| 5 cc. | 0.005 Gm. | 4.08 | $p_H$ of mixture 1.80 |
| 10 cc. | 0.010 Gm. | 5.00 | Time, 30 min. |
| 15 cc. | 0.015 Gm. | 8.20 | Pepsin A |
| 20 cc. | 0.020 Gm. | 10.20 | |

The method appears to be promising. The end-point, however, is uncertain, due to the rapid return of the red color of Phenolphthalein, after the first colorless end-point is reached. This can be rectified by titrating rapidly. In spite of the inaccuracies of the end-points a straight line relationship is indicated within the limits (0.005 to 0.200 Gm. pepsin).

A second series of determinations by this method gave results as follows:

TABLE XIII.

| Sample. | | Cc. 0.1*N* HCl (Difference). | Comments. |
|---|---|---|---|
| 10 cc. (inactive)* | | 0.14 | Casein 5.0 Gm. |
| 5 cc. | 0.005 Gm. | 2.30 | $p_H$ 1.80 |
| 10 cc. | 0.010 Gm. | 3.98 | Time, 30 min. |
| 15 cc. | 0.015 Gm. | 7.70 | Pepsin A |
| 20 cc. | 0.020 Gm. | 8.92 | |
| 25 cc. | 0.025 Gm. | 12.88 | |
| 50 cc. | 0.050 Gm. | 18.36 | |

* Sample of pepsin inactivated by heating to boiling.

The straight line relationship as found in the first series of determinations (Table XII) was confirmed, and with fair agreement, except for samples of pepsin containing less than 0.010 Gm. The end-points were still a source of considerable difficulty, and checks were difficult.

For a different sample of pepsin the straight line relationship was again determined between the limits of 0.005 and 0.025 Gm. of pepsin.

TABLE XIV.

| Sample. | | Cc. 0.1*N* HCl (Difference). | Comments. |
|---|---|---|---|
| 10 cc. (inactive)* | | 0.03 | Casein 3.0 Gm. |
| 5 cc. | 0.005 Gm. | 3.68 | $p_H$ 1.85 |
| 10 cc. | 0.010 Gm. | 6.20 | Time, 30 min. |
| 15 cc. | 0.015 Gm. | 8.74 | Pepsin B |
| 20 cc. | 0.020 Gm. | 11.44 | |
| 25 cc. | 0.025 Gm. | 13.62 | |
| 50 cc. | 0.050 Gm. | 14.84 | |
| 100 cc. | 0.100 Gm. | 15.84 | |

* Sample of pepsin inactivated by boiling.

In these determinations the amount of casein used was decreased to three Gm., the result being that the end-points were more readily determined.

The next determination was carried out with the reduced amount of casein, and the results were as follows:

TABLE XV.

| Sample. | | Cc. 0.01*N* HCl (Difference). | Comments. |
|---|---|---|---|
| 5 cc. | 0.005 Gm. | 2.96 | Casein 3.0 Gm. |
| 10 cc. | 0.010 Gm. | 4.32 | $p_H$ 1.85 |

| | | | |
|---|---|---|---|
| 15 cc. | 0.015 Gm. | 6.64 | Time, 30 min. |
| 20 cc. | 0.020 Gm. | 8.46 | Pepsin A |
| 25 cc. | 0.025 Gm. | 9.40 | |

Since Pepsin A is the reference standard, by means of the Schütz-Borrissov Rule, the proteolytic value of Pepsin B may be calculated. The values obtained in Tables XIV and XV are plotted and the straight lines drawn. Values obtained from the graph are given in the following table, and also by application of the equation the proteolytic value of Pepsin B was determined.

TABLE XVI.

| Pepsin A. | | Pepsin B. | | |
|---|---|---|---|---|
| | Proteolytic Activity | | Proteolytic Activity. | |
| Gm. | (Standard). | Gm. | From Curve. | By Equation. |
| 0.005 | 92% | 0.005 | 134 | 198 |
| 0.010 | 92% | 0.010 | 128 | 177 |
| 0.015 | 92% | 0.015 | 125 | 169 |
| 0.020 | 92% | 0.020 | 123 | 165 |

The proteolytic activity of Pepsin B having been determined to be about 115 per cent, it would appear that the Schütz-Borrissov Equation is not applicable when the time of digestion is short in fact, when using the equation the time is always taken as 24 hours. The values obtained from a comparison of the straight line relationships agree within 10 per cent.

Following the same procedure as in the preceding determinations, several samples of Pepsin A and Pepsin B of 0.020 Gm. each were assayed with the following results.

TABLE XVII.

| Pepsin A. | | Pepsin B. | |
|---|---|---|---|
| Cc. 0.1*N* HCl (Difference). | Proteolytic Activity (Standard). | Cc. 0.1*N* HCl (Difference). | Proteolytic Activity (Comparison). |
| 8.78 | 92% | 10.36 | |
| 8.26 | 92% | 10.96 | $(10.88/8.51) \times 92 = 118\%$ |
| 8.44 | 92% | 11.44 | |
| 8.24 | 92% | 10.74 | |
| 8.40 | 92% | | |
| 8.92 | 92% | Ave. 10.88 | |
| Ave. 8.51 | | | |

A series of determinations, all checking within 10 per cent, indicate a proteolytic activity of 118 per cent for Pepsin B compared with the 115 per cent experimentally determined.

National Formulary Preparations were next assayed by the same procedure. The preparations were removed from storage (at 15° C.) warmed to 20° C. and a portion taken, such that when diluted with pure distilled water, 20 cc. would contain 0.020 Gm. of Pepsin A.

TABLE XVIII.

| | Cc. 0.1*N* HCl (Difference). | | |
|---|---|---|---|
| Preparation. | I. | II. | Proteolytic Activity (Comparison). |
| Pepsinium Saccharatum | 8.30 | 8.56 | 88 |
| Elixir Pepsini | 5.72 | 6.16 | 62 |
| Liquor Pepsini | 7.58 | 7.28 | 82 |
| Liquor Pepsini Aromaticus | 7.32 | 6.78 | 79 |
| Glyceritum Pepsini | 7.84 | 6.82 | 85 |
| Elixir Pepsini et Bismuthi | 8.46 | | 91 |
| Elixir Pepsini et Rennini Comp. | 9.80 | | 106 |
| Elixir Pepsini Bismuthi et Strychninæ | 7.56 | | 82 |
| Pepsin A (ave. of 8 determinations) | 8.51 | | 92 (by exp.) |

Most of the preparations show a decreased proteolytic activity due to agitation and storage. (They were 6 months old.) Pepsinium Saccharatum gives an average of 91 per cent which

checks well with 92 per cent for the Pepsin A. Elixir Pepsini et Bismuthi and also Elixir Pepsini et Rennini Comp. were but a month old which would account for the higher values obtained.

This method as developed, appears to be applicable to pepsin and pepsin containing preparations of the National Formulary. It is as accurate as the egg-albumen digestion method, when applied to pepsin itself, and checks within 10 per cent are obtained with pepsin preparations. The method is simple, and a complete assay can be performed in about an hour. The greatest difficulty is an accurate determination of the end-point of the titration. It is believed that this can be solved by further study, which is contemplated.

## CONCLUSIONS.

1. Pepsin containing preparations of The National Formulary are extensively prescribed in modern pharmacy.
2. The Assay of Pepsin as proposed by Greenberg is not practicable for the assay of pepsin containing preparations.
3. Assay methods based on proteolytic digestion of casein and subsequent blocking-off of the amino group, are inapplicable to pepsin or pepsin containing preparations.
4. The Schütz-Borrissov Rule for proteolytic digestion of casein is inaccurate when the time of digestion is short.
5. A modified Volhard's Method has been developed which will permit the measurement of proteolytic activity in pepsin or pepsin containing preparations, within 10 per cent or less.
6. The method developed is rapid and simple, except for the end-point of the titration.

## ACKNOWLEDGMENT.

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## THE PHARMACOLOGICAL ACTION OF PEIMINE AND PEIMININE.*

BY K. K. CHEN, A. LING CHEN AND T. Q. CHOU.

The crude drug, Pei Mu, has been used in Chinese medicine as an antipyretic, cough sedative, expectorant and lactagogue (1). In combination with other ingredients, it has been advocated for the treatment of difficult labor, retention of placenta, blurring of vision and spider and snake bites.

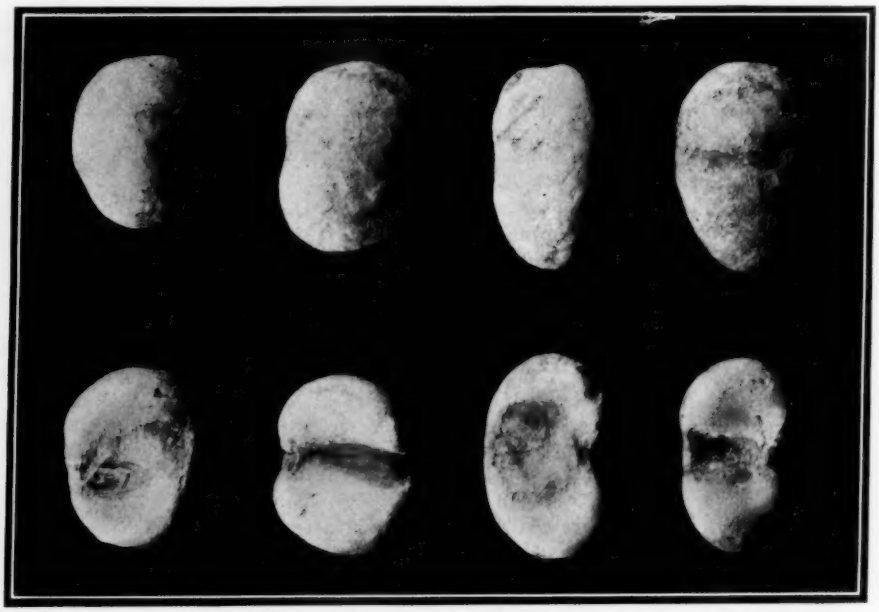

Fig. 1.—Pei Mu from Chekiang Province.

Pei Mu is made of the bulbs or corms of a liliaceous plant which is identified as *Fritillaria roylei* by Stuart (2), but as *F. verticillata*, Willd. *var. Thunbergii*, Bak. in Botanical Nomenclature (3). The corms produced in Chekiang Province are kidney-shaped, as shown in Fig. 1, each weighing on the average 3.5 Gm., and

* From the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, and the Institute of Materia Medica, National Academy of Peiping, and the Sino-French University, Peiping, China.

measuring 1.9 cm. in width and 2.8 cm. in length. Those grown in Szechuan Province and other localities are different in size and shape. It is possible that in Chinese commerce several varieties or species come under the same name, Pei Mu.

Yagi in 1913 (4) reported the isolation from Pei Mu of a base having the formula $C_{25}H_{41}NO_3.H_2O$ which he named *fritilline*. This substance forms no salts with acids. It is said to depress the respiration and heart action similarly to veratrine.

In contrast to the results of Yagi, Fukuda (5) obtained two different crystalline substances: *verticine*, $C_{18}H_{33}O_2N$ or $C_{19}H_{35}O_2N$, m. p. 224–224.5° C., $[\alpha]_D^{10}$ −10.66°; and *verticilline*, $C_{19}H_{33}O_2N$, m. p. 148–150° C.

In a previous communication (6) one of us (T. Q. C.) described the isolation of two alkaloids from the material of Chekiang origin. Although the two principles

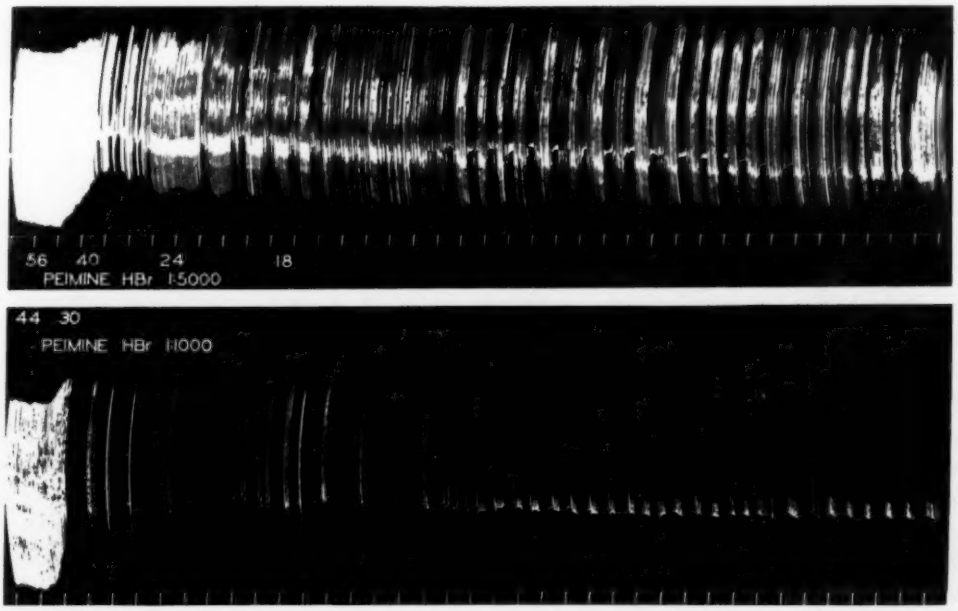


Fig. 2.—Action of Peimine HBr on Frog's Heart. Upper: Frog No. 222, male, weighing 44 Gm., pithed. Lower: Frog No. 219, female, weighing 50 Gm., pithed.

have some resemblance in elementary composition to verticine and verticilline, they do not seem to be entirely identical with the latter, thus justifying the proposal of two new names: *peimine*, $C_{19}H_{30}NO_2$, m. p. 223° C., $[\alpha]_D^{24}$ 0°; and *peiminine*, $C_{18}H_{28}NO_2$, m. p. 135° C., $[\alpha]_D^{24}$ −62.5°.

The present paper deals with the pharmacological effects of peimine and peiminine. The hydrobromides of the two substances were employed in all experiments—peimine HBr melting at 288° C. and peiminine HBr at 292° C.

*A. In Frogs.*—The action of both peimine and peiminine is practically identical. In small frogs (20 to 21 Gm.) doses of 5 to 10 mg. of either substance injected into the lymph sac produced no toxic signs. When perfused through the inferior vena cava, a 0.1 per cent solution of peimine HBr rapidly caused slowing of heart rate, increase in systole and decrease in diastole, soon followed by almost complete

A-V block, as shown in Fig. 2. The ventricle became so depressed that it contracted only at intervals, and gradually the amplitude grew very small. A concentration of 1:5000 reacted in a similar but less effective manner (Fig. 2). Periodicity was the ultimate feature. The results with peiminine are essentially the same.

*B. Toxicity.*—By intravenous injection in mice of a 0.1 per cent solution of either peimine HBr or peiminine HBr, the minimal lethal dose was determined to be 9 mg. per Kg. for each, as summarized in Table I. Violent tonic convulsions occurred before death. Doses as small as 3 or 4 mg. per Kg. also caused convulsive movements which became more pronounced upon stimulation. Those animals that survived showed no apparent injury when observed for 7 to 10 days.

TABLE I.—TOXICITY OF PEIMINE HBr AND PEIMININE HBr IN MICE BY INTRAVENOUS INJECTION (SOLUTION 0.1 PER CENT).

| Drug. | Dose, Mg. per Kg. | Number of Mice Used. | Number of Mice Died. | Minimal Lethal Dose, Mg. per Kg. |
|---|---|---|---|---|
| Peimine HBr | 8 | 5 | 2 | |
| | 9 | 5 | 3 | 9 |
| | 10 | 5 | 4 | |
| Peiminine HBr | 8 | 5 | 1 | |
| | 9 | 5 | 4 | 9 |
| | 10 | 1 | 1 | |
| | 11 | 3 | 2 | |

In rats the toxicity, as tested with peimine HBr, is not so great, although convulsions were noticed with a dose of 5 mg. per Kg., injected intravenously. These animals completely recovered from an amount of 25 mg., but deaths began to occur with a dose of 35 mg. per Kg. No study was made with peiminine in rats.

In rabbits, weakness in the legs, ataxia and tremulous movements occurred following a dose of 10 mg. per Kg., given by vein, of either peimine or peiminine in the form of a hydrobromide.

*C. Other Effects.*—Both peimine and peiminine as hydrobromides in the dosage of 10 or more mg. produced a fall of blood pressure, with prompt recovery, in etherized cats. The amplitude of the respiration diminished slightly as the blood pressure fell.

In rabbits there was a moderate hyperglycemia following the intravenous administration of either peimine or peiminine. Thus one animal had an increase of 71 mg. of sugar per 100 cc. of blood 45 minutes after the injection of 10 mg. of peiminine HBr. The maximal increase in another rabbit with 5 mg. of peiminine HBr was 14 mg. Peimine HBr caused a maximal rise of blood sugar of 23 mg. per 100 cc. of blood in a rabbit with a dose of 10 mg., 22 mg. in another with a dose of 7.5 mg. per Kg. and 18 and 35 mg. in two others with doses of 5 mg. per Kg. each.

A concentration of 1:10,000 of peimine or peiminine HBr inhibited the movements of rabbits' isolated intestines, with gradual recovery.

When applied locally a 1 per cent solution of either substance is slightly bitter to the taste, the action of peimine HBr being somewhat more pronounced. No mydriasis or local anesthesia resulted when the same solution was dropped into rabbits' eyes. Neither peimine nor peiminine stimulated the submaxillary and pancreatic secretions, or increased the urinary output (dogs).

SUMMARY.

The effects produced by peimine and peiminine are practically the same. When perfused through the inferior vena cava in frogs, they induce decrease in the heart rate, complete A-V block and periodicity. They cause a fall of blood pressure (cats), and inhibit the activity of isolated rabbits' intestines. There is a moderate hyperglycemic action in rabbits. The minimal lethal dose to white mice, by intravenous injection, of both peimine and peiminine, is 9 mg. per Kg., death being preceded by tonic convulsions.

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# STUDIES IN PERCOLATION.*

## A. Anomalies Observed in the Percolation of Cinchona.

BY MILTON WRUBLE.

As one of the first tests of the mechanism of percolation, it seemed desirable to learn something about the nature of the extraction as the menstruum passes down from stratum to stratum in the percolator. The ideal way to carry out this test experimentally on a percolator containing 1000 Gm. of drug, would be to segment the drug in layers of 100 Gm. and stop the tincture at the bottom of each segment. To carry out this idea practically it seemed unsatisfactory to devise a means giving even approximate results. Hence, in place of a single percolator, a number of percolators were used, each representing a hypothetical segment of the larger percolator as suggested above.

The unit adopted for the first test of this scheme was that of 100 Gm. and the unit of percolate to be tested that of 100 cc. Inasmuch as 10 cc. were to be removed from each percolate for the tests planned, it was necessary to charge the second percolator with 90 Gm. of drug and to draw 90 cc. of percolate, to charge the third percolator with 80 Gm. of drug and to draw 80 cc. of percolate, etc.

Cinchona was selected for this experiment, not only because its alkaloidal content could be determined quantitatively with a considerable degree of accuracy even in mere traces, but because this drug presented problems in connection with the keeping qualities of both tincture and fluidextract that were worth while investigating.

The drug in question was obtained from J. L. Hopkins & Co., in December 1930, in powdered form, approximately a No. 20 powder.

*Experiment I.*—The 100-Gm. batch was moistened with 75 cc. of 95 p. c. alcohol, and the other batches with equivalent amounts. Each such moistened batch was allowed to stand in a closed container for 6 hours before packing in the per-

* Scientific Section, A. Ph. A., Toronto meeting, 1932.

colator. After packing, maceration was allowed to take place for 24 hours before percolation was commenced.[1] In the case of the 100-Gm. batch the drawing off of the percolate lasted approximately 200 minutes. In other cases corresponding periods were allowed.

As already indicated 10 cc. of percolate were set aside in each case. Of this reserved portion, 5 cc. were allowed to evaporate spontaneously at room temperature until of constant weight in order to determine the amount of extractive. The other 5 cc. were used for density determination by means of a pycnometer and for alkaloidal assay. The latter was carried out with modifications,[1] according to the U. S. P. X process described under Fluidextract of Cinchona. The results are herewith tabulated:

| Amt. of Drug, Gm. | Rate of Percolation,[1] Minutes. | Sp. Gr., 20°. | Extractive, | | Total Alkaloids,[2] | |
|---|---|---|---|---|---|---|
| | | | Wt., Gm. | Per Cent. | Wt., Gm. | Per Cent. |
| 100 | 200 | 0.852 | 0.59 | 13.8 | 0.02 | 0.59 |
| 90 | 180 | 0.864 | 0.75 | 17.3 | 0.01 | 0.29 |
| 80 | 160 | 0.876 | 0.89 | 20.3 | 0 008 | 0 23 |
| 70 | 140 | 0.876 | 0.97 | 22.2 | 0.01 | 0.29 |
| 60 | 120 | 0.866 | 0.81 | 18.7 | 0.02 | 0.59 |
| 50 | 100 | 0.856 | 0.64 | 14.9 | 0.02 | 0.59 |

[1] The rate was set at as close to ten drops per minute as was possible and from time to time this rate had to be increased or decreased to this figure.

[2] No alkaloidal assay on this bark was made.

*Experiment IIa.*—A second series of percolators was started, this time using ten and following out the same general scheme as in the first set of experiments. In each case the material was macerated for twenty-four hours in the percolator before the actual percolation, as before.

The results are tabulated as follows:

| Amt. of Drug, Gm. | Rate,[1] Minutes. | Sp. Gr., 20°. | Extractive, | | Total Alkaloids, | |
|---|---|---|---|---|---|---|
| | | | Wt., Gm. | Per Cent. | Wt., Gm. | Per Cent. |
| 100 | 200 | 0.835 | 0.45 | 10.7 | 0.03 | 0 89 |
| 90 | 180 | 0 856 | 0.64 | 14.9 | 0.02 | 0.58 |
| 80 | 160 | 0.863 | 0.80 | 18.5 | 0.02 | 0.57 |
| 70 | 140 | 0.884 | 0.90 | 20.4 | 0.02 | 0.56 |
| 60 | 120 | 0.880 | 0.87 | 19.7 | 0.02 | 0.57 |
| 50 | 100 | 0.868 | 0.86 | 19.8 | 0.03 | 0.86 |
| 40 | 80 | 0.866 | 0.84 | 18.9 | 0.07 | 2.02 |
| 30 | 60 | 0.885 | 0.80 | 18.2 | 0.05 | 1.41 |
| 20 | 40 | 0.887 | 0.87 | 19.6 | 0.06 | 1.41 |
| 10 | 20 | 0.863 | 0.58 | 13.4 | 0.06 | 1.73 |

[1] The rate was set as close to ten drops per minute as was possible. Invariably the rate slowed down and required frequent attention. In the case of the 100-Gm. and 90-Gm. percolators the percolation stopped several times unexpectedly hence the time in these two cases is approximate.

*Experiment IIb.*—Extraction was resumed September 24th on the same set of percolators used in Experiment IIa after they had been corked and left standing since June 14th. The same general scheme was followed out in this case as before. The results are tabulated as follows:

[1] No absorbent material was used but the alcoholic extract added directly to the ether-chloroform mixture.

| Amt. of Drug, Gm. | Rate, Hours. | Sp. Gr., 20°. | Extractive,[1] Wt., Gm. | Extractive,[1] Per Cent. | Total Alkaloids,[2] Wt., Gm. | Total Alkaloids,[2] Per Cent. |
|---|---|---|---|---|---|---|
| 100 | 18½ | 0.796 | 0.15 | 3.7 | 0.02 | 0.63 |
| 90 | 18 | 0.803 | 0.30 | 7.4 | 0.03 | 0.93[3] |
| 80 | 12½ | 0.814 | 0.31 | 7.6 | 0.04 | 1.22 |
| 70 | 11¼ | 0.828 | 0.39 | 9.4 | 0.055 | 1.66 |
| 60 | 9¼ | 0.820 | 0.44 | 10.7 | 0.05 | 1.52 |
| 50 | 6¾ | 0.830 | 0.46 | 11.0 | 0.05 | 1.50 |
| 40 | 4 | 0.840 | 0.55 | 13.0 | 0.06 | 1.64 |
| 30 | 3¼ | 0.828 | 0.45 | 10.8 | 0.05 | 1.50 |
| 20 | 2¾ | 0.825 | 0.37 | 8.9 | 0.04 | 1.21 |
| 10 | 2 | 0.822 | 0.47 | 11.4 | 0.03 | 0.91 |

[1] U. S. P. X method for total extractive, page 466.

[2] U. S. P. X method for total alkaloids, page 453.

[3] No doubt the increases in these alkaloidal contents are due to the maceration period which intervened.

*Experiment III.*—The same scheme as had been carried out with the smaller quantities was now extended to larger quantities of drug.[1] In the first percolator 1000 Gm. of drug were used, in the second 900 Gm. and so on to the tenth percolator containing 100 Gm. From the percolator containing 1000 Gm., 1000 cc. of tincture were collected, 100 cc. of this amount were reserved and the 900 cc. of the remaining tincture used in percolating the next batch containing 900 Gm. of drug. This was repeated throughout just as was done in the earlier experiments. Ten such series of experiments were made and the determinations carried out as outlined in the U. S. P. X.

$p_H$ determinations were attempted with the use of the quinhydrone electrode in conjunction with a Leeds and Northrup potentiometer set-up. Because of the high alcoholic content of the solutions these values are not to be relied upon.[2] The results of ten such series of extractions are herewith tabulated:

SERIES I.

| Amt. of Drug, Gm. | $p_H$.[1] | Rate, Hours. | Sp. Gr., 20°. | Extractive,[2] Wt., Gm. | Extractive,[2] Per Cent. | Alkaloidal Content,[2] Wt., Gm. | Alkaloidal Content,[2] Per Cent. |
|---|---|---|---|---|---|---|---|
| 1000 | 3.72 | 78¾ | 0.8572 | 0.772 | 9.05 | 0.04 | 1.17 |
| | 3.27 | | | | | | |
| 900 | 3.87 | 71¼ | 0.8699 | 1.03 | 11.09 | 0.54 | 1.59 |
| | 3.52 | | | | | | |
| 800 | 4.22 | 61½ | 0.8703 | 1.10 | 12.50 | 0.55 | 1.58 |
| | 3.44 | | | | | | |
| 700 | 3.98 | 52¾ | 0.8725 | 1.14 | 13.00 | 0.56 | 1.63 |
| | 3.28 | | | | | | |
| 600 | 3.75 | 48½ | 0.8787 | 1.27 | 14.50 | 0.58 | 1.63 |
| | 3.32 | | | | | | |
| 500 | 3.69 | 41 | 0.8685 | 1.14 | 13.20 | 0.53 | 1.54 |
| | 3.32 | | | | | | |
| 400 | 3.80 | 34¾ | 0.8691 | 1.07 | 12.40 | 0.53 | 1.53 |
| | 3.77 | | | | | | |
| 300 | 3.78 | 22½ | 0.8691 | 1.07 | 12.65 | 0.48 | 1.41 |
| | 3.73 | | | | | | |

[1] Received from J. L. Hopkins & Co. in 1931, No. 20 powder, alkaloidal assay 4.70 p. c., 4.32 p. c. and 4.26 p. c. of total alkaloids in as many assays (U. S. P. X).

[2] It is possible that the apparatus did not admit of the sensitivity that should be required when working under such conditions.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 200 | 4.12<br>3.73 | 13½ | 0.8681 | 1.14 | 13.24 | 0.52 | 1.50 |
| 100 | 4.26<br>3.80 | 7¾ | 0.8761 | 1.38 | 15.80 | 0.61 | 1.74 |

[1] The second figures in the $p_H$ column were obtained 72 hours after the first readings were taken.

[2] The total extractive was determined by drying in an oven exactly as outlined in the U. S. P. X and not as was carried out in earlier experiments. Alkaloidal determinations were also made according to U. S. P. X methods.

SERIES II.

| Amt. of Drug, Gm. | $p_H$. | Rate, Hours. | Sp. Gr., 20°. | Extractive, Wt., Gm. | Extractive, Per Cent. | Alkaloidal Content, Wt., Gm. | Alkaloidal Content, Per Cent. |
|---|---|---|---|---|---|---|---|
| 1000 | 3.80<br>3.15 | 77¼ | 0.8320 | 0.310 | 3.72 | 0.02 | 0.60 |
| 900 | 3.90<br>3.12 | 72½ | 0.8555 | 0.714 | 8.35 | 0.031 | 0.91 |
| 800 | 4.24<br>3.65 | 62¾ | 0.8613 | 0.926 | 10.67 | 0.045 | 1.33 |
| 700 | 4.22<br>3.73 | 50½ | 0.8612 | 0.911 | 10.60 | 0.042 | 1.24 |
| 600 | 3.92<br>3.46 | 47½ | 0.8616 | 0.878 | 10.11 | 0.035 | 1.02 |
| 500 | 3.95<br>3 35 | 37¾ | 0.8519 | 0.749 | 8.75 | 0.027 | 0.79 |
| 400 | 3.95<br>3.25 | 32¼ | 0.8489 | 0.685 | 8.10 | 0.024 | 0.71 |
| 300 | 4.02<br>3.31 | 24 | 0.8508 | 0.743 | 8.75 | 0.031 | 0.93 |
| 200 | 4.15<br>3.31 | 10¾ | 0.8549 | 0.803 | 9 40 | 0.028 | 0.82 |
| 100 | 4.02<br>3.22 | 6½ | 0.8555 | 0.793 | 9.30 | 0.034 | 0.01 |

SERIES III.

| Amt. of Drug, Gm. | $p_H$. | Rate, Hours. | Sp. Gr., 20°. | Extractive, Wt., Gm. | Extractive, Per Cent. | Alkaloidal Content, Wt., Gm. | Alkaloidal Content, Per Cent. |
|---|---|---|---|---|---|---|---|
| 1000 | 4.20<br>3.87 | 76¼ | 0.8177 | 0.167 | 2.05 | 0.013 | 0.39 |
| 900 | 3.72<br>3.73 | 70 | 0.8240 | 0.256 | 3.10 | 0.020 | 0.62 |
| 800 | 3.97<br>4 05 | 58½ | 0.8339 | 0.437 | 5.23 | 0.027 | 0.81 |
| 700 | 4.04<br>4.10 | 51¼ | 0.8335 | 0.491 | 5.88 | 0.033 | 0.99 |
| 600 | 4.17<br>3.82 | 42½ | 0.8379 | 0.414 | 5.95 | 0.023 | 0.69 |
| 500 | 3.93<br>3.68 | 38½ | 0.8387 | 0.512 | 6.12 | 0.026 | 0.78 |
| 400 | 3.76<br>3.40 | 30¾ | 0.8334 | 0.426 | 5.12 | 0.038 | 0.84 |
| 300 | 3.67<br>3.58 | 22½ | 0.8329 | 0.394 | 4.72 | 0.021 | 0.65 |
| 200 | 3.72<br>3.47 | 14½ | 0.8335 | 0.434 | 5.20 | 0.022 | 0.68 |
| 100 | 4.21<br>3.96 | 8½ | 0.8349 | 0.574 | 6.87 | 0.025 | 0.76 |

SERIES IV.

| Amt. of Drug, Gm. | $p_H$. | Rate, Hours. | Sp. Gr., 20°. | Extractive, Wt., Gm. | Extractive, Per Cent. | Alkaloidal Content, Wt., Gm. | Alkaloidal Content, Per Cent. |
|---|---|---|---|---|---|---|---|
| 1000 | 3.78<br>3.74 | 58¾ | 0.8167 | 0.124 | 1.52 | 0.010 | 0.30 |
| 900 | 3.53<br>3.57 | 49½ | 0.8217 | 0.234 | 2.84 | 0.015 | 0.47 |
| 800 | 3.53<br>3.20 | 44½ | 0.8312 | 0.372 | 4.46 | 0.023 | 0.69 |
| 700 | 3.63<br>3.20 | 40 | 0.8337 | 0.432 | 5.10 | 0.021 | 0.65 |
| 600 | 3.35<br>3.57 | 37¼ | 0.8347 | [1] | | 0.025 | 0.76 |
| 500 | 3.36<br>3.15 | 34½ | 0.8368 | 0.493 | 5.90 | 0.034 | 0.77 |
| 400 | 3.18<br>3.07 | 28½ | 0.8368 | 0.477 | 5.70 | 0.025 | 0.79 |
| 300 | 3 22<br>3.10 | 23¼ | 0 8323 | 0.385 | 4.74 | 0.024 | 0.72 |
| 200 | 3.15<br>3.48 | 16¾ | 0.8307 | 0.391 | 4.72 | 0.023 | 0.70 |
| 100 | 3.47<br>3.48 | 9 | 0.8412 | 0.582 | 6.90 | 0.027 | 0.80 |

[1] Sample lost.

SERIES V.

| Amt. of Drug, Gm. | $p_H$. | Rate, Hours. | Sp. Gr., 20°. | Extractive, Wt., Gm. | Extractive, Per Cent. | Alkaloidal Content, Wt., Gm. | Alkaloidal Content, Per Cent. |
|---|---|---|---|---|---|---|---|
| 1000 | 3.58<br>3.52 | 50½ | 0.8148 | 0.095 | 1.16 | 0.013 | 0.41 |
| 900 | 3.29<br>3.56 | 44¾ | 0.8210 | 0.164 | 2.01 | 0.015 | 0.47 |
| 800 | 3.14<br>3.93 | 41½ | 0.8267 | 0.273 | 3.32 | 0.025 | 0.77 |
| 700 | 3.22<br>3.88 | 39¾ | 0.8320 | 0.387 | 4.64 | 0.026 | 0.79 |
| 600 | 3.54<br>3.85 | 36½ | 0.8344 | 0.453 | 5.42 | 0.020 | 0.61 |
| 500 | 3.34<br>3.68 | 34½ | 0.8371 | 0.493 | 5.88 | 0.020 | 0.61 |
| 400 | 3.44<br>3.87 | 26¼ | 0.8371 | 0.514 | 6.15 | 0.032 | 0.97 |
| 300 | 3.23<br>3.77 | 22¼ | 0.8336 | 0.450 | 5.40 | 0.021 | 0.64 |
| 200 | 3.26<br>3.62 | 14¾ | 0.8325 | 0.407 | 4.88 | 0.017 | 0.51 |
| 100 | 3.42<br>3.75 | 8½ | 0.8353 | 0.472 | 5.65 | 0.025 | 0.76 |

SERIES VI.

| Amt. of Drug, Gm. | $p_H$. | Rate, Hours. | Sp. Gr., 20°. | Extractive, Wt., Gm. | Extractive, Per Cent. | Alkaloidal Content, Wt., Gm. | Alkaloidal Content, Per Cent. |
|---|---|---|---|---|---|---|---|
| 1000 | 3.87<br>4.10 | 53 | 0.8131 | 0.075 | 0.93 | 0.009 | 0.29 |
| 900 | 3.67<br>4.10 | 47½ | 0.8169 | 0.140 | 1.70 | 0.010 | 0.31 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 800 | 3.52<br>4.23 | 44 1/2 | 0.8253 | 0.235 | 2.85 | 0.016 | 0.48 |
| 700 | 3.26<br>4.55 | 41 | 0.8303 | 0.382 | 4.60 | 0.023 | 0.54 |
| 600 | 3.34<br>3.07 | 36 1/4 | 0.8349 | 0.452 | 5.42 | 0.021 | 0.64 |
| 500 | 3.28<br>3.32 | 32 3/4 | 0.8367 | 0.477 | 5.70 | 0.022 | 0.66 |
| 400 | 3.38<br>3.35 | 27 1/4 | 0.8364 | 0.531 | 6.35 | 0.023 | 0.71 |
| 300 | 4.13<br>3.35 | 23 3/4 | 0.8345 | 0.470 | 5.62 | 0.023 | 0.70 |
| 200 | 3.55<br>3.75 | 17 3/4 | 0.8343 | 0.478 | 5.72 | 0.022 | 0.67 |
| 100 | 3.61<br>3.87 | 8 3/4 | 0.8336 | 0.425 | 5.10 | 0.023 | 0.69 |

SERIES VII.

| Amt. of Drug, Gm. | $p_H$. | Rate, Hours. | Sp. Gr., 20°. | Extractive, Wt. Gm. | Extractive, Per Cent. | Alkaloidal Content, Wt. Gm. | Alkaloidal Content, Per Cent. |
|---|---|---|---|---|---|---|---|
| 1000 | 3.32<br>3.67 | 52 1/2 | 0.8096 | 0.058 | 0.72 | 0.008 | 0.24 |
| 900 | 3.28<br>3.80 | 45 1/2 | 0.8145 | 0.119 | 1.46 | 0.012 | 0.37 |
| 800 | 2.98<br>3.87 | 43 | 0.8188 | 0.197 | 2.40 | 0.016 | 0.59 |
| 700 | 3.00<br>3.62 | 41 3/4 | 0.8242 | 0.300 | 3.63 | 0.020 | 0.62 |
| 600 | 3.45<br>3.47 | 37 1/4 | 0.8296 | 0.427 | 5.18 | 0.024 | 0.72 |
| 500 | 3.23<br>3.65 | 34 1/4 | 0.8320 | 0.463 | 5.45 | 0.026 | 0.78 |
| 400 | 3.26<br>3.42 | 25 3/4 | 0.8345 | 0.521 | 6.25 | 0.027 | 0.81 |
| 300 | 3.22<br>3.50 | 22 1/2 | 0.8336 | 0.512 | 6.15 | 0.027 | 0.82 |
| 200 | 3.42<br>3.38 | 19 1/4 | 0.8298 | 0.428 | 5.12 | 0.026 | 0.79 |
| 100 | 3.49<br>3.43 | 7 3/4 | 0.8318 | 0.457 | 5.50 | 0.028 | 0.86 |

SERIES VIII.

| Amt. of Drug, Gm. | Rate, Hours. | Sp. Gr. 20°. | Extractive, Wt. Gm. | Extractive, Per Cent. | Alkaloidal Content, Wt. Gm. | Alkaloidal Content, Per Cent. |
|---|---|---|---|---|---|---|
| 1000 | 50 3/4 | 0.8098 | 0.043 | 0.54 | 0.008 | 0.24 |
| 900 | 44 1/2 | 0.8138 | 0.115 | 1.42 | 0.017 | 0.32 |
| 800 | 41 1/2 | 0.8175 | 0.183 | 2.23 | 0.0125 | 0.38 |
| 700 | 37 1/2 | 0.8226 | 0.275 | 3.33 | 0.0200 | 0.60 |
| 600 | 34 1/4 | 0.8302 | 0.415 | 5.00 | 0.022 | 0.68 |
| 500 | 30 | 0.8321 | 0.483 | 5.80 | 0.025 | 0.74 |
| 400 | 27 1/4 | 0.8346 | 0.570 | 6.82 | 0.027 | 0.82 |
| 300 | 23 1/2 | 0.8352 | 0.565 | 6 70 | 0.022 | 0.67 |
| 200 | 18 1/4 | 0.8342 | 0.535 | 6.40 | 0.026 | 0.79 |
| 100 | 8 1/2 | 0.8386 | 0.584 | 7.00 | 0.028 | 0.83 |

SERIES IX.

| Amt. of Drug, Gm. | Rate, Hours. | Sp. Gr., 20°. | Extractive, Wt. Gm. | Extractive, Per Cent. | Alkaloidal Content. Wt. Gm. | Alkaloidal Content. Per Cent. |
|---|---|---|---|---|---|---|
| 1000 | 44 1/2 | 0.8183 | 0.038 | 0.47 | 0.008 | 0 24 |
| 900 | 41 1/4 | 0 8198 | 0.075 | 0.92 | 0.0085 | 0.26 |
| 800 | 37 1/4 | 0.8229 | 0.1345 | 1.63 | 0.0130 | 0.39 |
| 700 | 34 | 0.8268 | 0.209 | 2.53 | 0.0190 | 0.59 |
| 600 | 32 1/2 | 0.8298 | 0.282 | 3.39 | 0.022 | 0.66 |
| 500 | 31 1/4 | 0.8373 | 0.408 | 4.87 | 0.024 | 0.72 |
| 400 | 26 3/4 | 0.8414 | 0.484 | 5.72 | 0.025 | 0.75 |
| 300 | 21 1/2 | 0.8519 | 0.736 | 8.65 | 0.031 | 0.90 |
| 200 | 11 1/2 | 0.8706 | 0.890 | 9.30 | 0.031 | 0.90 |
| 100 | 6 | 0.8598 | 0.763 | 8.90 | 0.029 | 0.86 |

SERIES X.[1]

| Amt. of Drug, Gm. | Rate, Hours. | Sp. Gr., 20°. | Extractive, Wt. Gm. | Extractive, Per Cent. | Alkaloidal Content, Wt. Gm. | Alkaloidal Content, Per Cent. |
|---|---|---|---|---|---|---|
| 1000 | 46 1/2 | 0.8162 | 0.038 | 0.46 | 0.006 | 0.18 |
| 900 | 40 | 0.8171 | 0.075 | 0.90 | 0.012 | 0.28 |
| 800 | 37 3/4 | 0.8213 | 0.119 | 1.44 | 0.016 | 0 48 |
| 700 | 33 | 0.8239 | 0.187 | 2.23 | 0.017 | 0.50 |
| 600 | 31 1/2 | 0.8224 | 0.190 | 2.32 | 0.013 | 0.39 |
| 500 | 27 3/4 | 0.8323 | 0.321 | 3.85 | 0.040 | 0.49 |
| 400 | 25 1/2 | 0.8310 | 0.355 | 4.26 | 0.022 | 0.66 |
| 300 | 20 | 0.8406 | 0.548 | 6.62 | 0.026 | 0.79 |
| 200 | 10 3/4 | 0.8403 | 0.472 | 5.62 | 0.016 | 0.47 |
| 100 | 7 1/4 | 0.8373 | 0.479 | 5.72 | 0.021 | 0.62 |

[1] The ninth and tenth series in these experiments were run after an approximately three-month period of rest.

*Discussion.*—From these many results it is to be noted that certain anomalies are present. In every series the maximum point is reached followed by a decrease. Such results are not readily explainable. No doubt, however, certain surface phenomena, such as adsorption, absorption and perhaps others of which we know little, are responsible in a great measure for this anomaly.

*Errors.*—These experiments presented a number of difficulties in technique some of which were only realized during the procedure. It must be admitted that at their best they represent only an approach to ideal conditions. While as many of the variables in percolation were controlled as nearly as possible to be identical in each of the ten percolators, it was found quite impossible to maintain them at comparative rates of flow for any length of time. The rates would generally decrease after being adjusted, sometimes increase and in a number of instances stop flowing altogether.

Where the rate decreased it was adjusted to run faster so that the final volumes in all percolators would be collected at comparative rates and if it increased the percolator was allowed to run slower in like manner. If a percolator stopped and was not noticed soon thereafter (this did not occur frequently), the rate at which it was set was determined by the judgment developed in carrying out the rather large number of extractions.

Percolators were started at approximately the same time each morning and stopped at a fixed time every day. Experimentation was not interrupted at any

other time but was carried out seven days a week. Here again, the ideal manner of conducting such extractions would have been to continue percolation from the very beginning without a single interruption. While we may assume that the intervening maceration periods, having been the same in each case would tend to equalize this error, it must not be forgotten that during these macerations numerous changes took place. (See Series IX and X.)

Throughout the many months in which these experiments were conducted the changes in temperature[1] must have affected the solubility of the constituents more or less. Some of the latter series were made in the warmer months of the year, the earlier in the fall months while those in between during the winter months. The room temperature during these various periods of the year must of necessity have varied somewhat.

In spite of the errors that have been enumerated it is believed that inasmuch as the large number of extractions made show strikingly the repetition that has already been pointed out, we can feel justified in believing that such an anomaly exists in the case of cinchona.

It was only after the experimental results had been tabulated that Searby's discussion of Seifert's paper on "interrupted" percolation (*Proc. Cal. Pharm. Soc.*, 22 (1892), 125) came to the notice of the writer. When a year ago the anomalies observed were discussed with Professor Wilbur Scoville and Dr. F. O. Taylor of Parke, Davis & Co., both stated that they had observed them in factory practice. Inasmuch as their observations have not been published, hence their data are not available, it seemed best to complete the series of experiments recorded above and to report in detail. No one appears to have attempted an explanation of these anomalies thus far. It certainly is imperative that they be given due consideration even though they complicate a situation already sufficiently difficult of understanding.

WISCONSIN PHARMACEUTICAL EXPERIMENT STATION.

[1] Goris, who has recently made a comprehensive theoretical analysis of percolation, states in this connection: *"Il est surtout important au cours d'une lixiviation, d'éviter les changements de temperature."* (*Bull. des Sciences Pharmcol.*, 26 (1919), 477.)

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## STRYCHNINE POISONING.

M. C. Wheelock (*J. A. M. A.*, 99 (1932), 1862) reports on a case of attempted suicide in which probably about 1 grain of strychnine sulphate was taken as recorded, in which the patient ultimately recovered under prompt treatment with sodium phenobarbital and sodium amytal. The immediate treatment, twenty minutes after the first seizure, was the administration of 5 grains of phenobarbital by hypodermic injection. Subsequent to this, any attempt to move the patient caused violent convulsions; 5 grains more sodium barbital was then injected by vein but without complete relief. Therefore, 15 grains of sodium amytal, dissolved in 10 cc. of water, was injected intravenously at the rate of 1 cc. a minute. The patient was sound asleep in ten minutes and could then be moved to bed. There were only slight spasms during the subsequent day. Further treatment consisted in the administration of the three bromides. Subsequently recovery was uneventful. No attempt was made to wash the stomach. The antidotal action of phenobarbital sodium on experimental strychnine poisoning in animals has been recorded previously, but no case of its use for this purpose in man has been recorded. In this one case the results were so dramatic as to suggest that the remedy should at least be tried when needed.—Through *Quarterly Journal of Pharmacy.*

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Compiled by A. G. DuMez, Reporter on the Progress of Pharmacy.

All articles in these lists will be presented in abstract form in the bound volumes of the Year Book, which is issued annually. Those desiring abstracts immediately can obtain them for a fee of one dollar each by communicating with A. G. DuMez, University of Maryland, School of Pharmacy, N. W. cor. Lombard and Greene Sts., Baltimore, Maryland.

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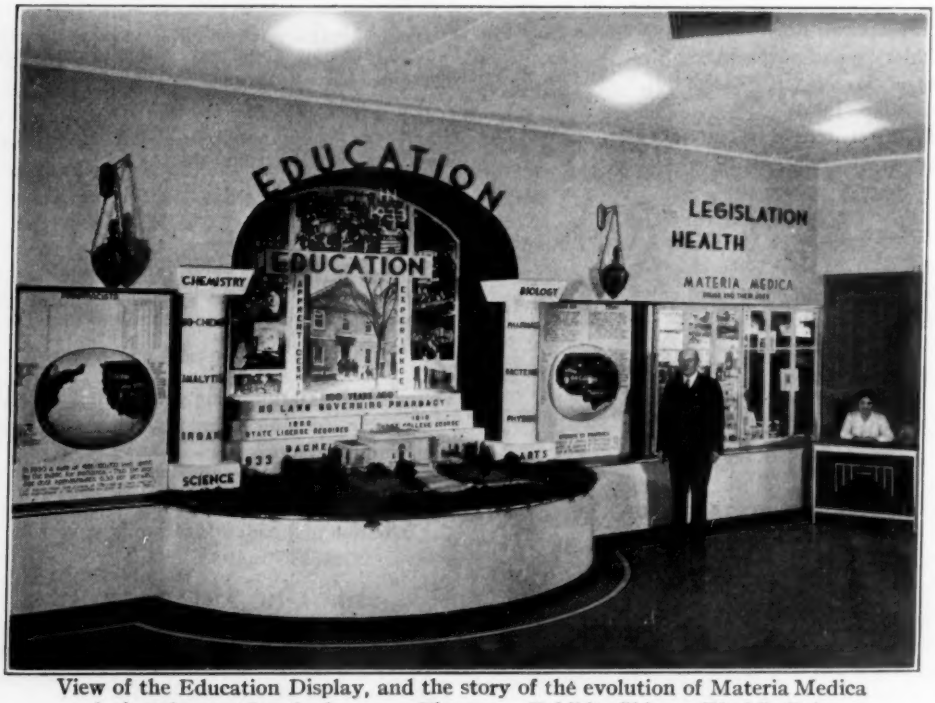
## WHAT IS A PROFESSION?

Justice Brandeis, of the United States Supreme Court, is credited with this definition of a profession:

"*First*, a profession is an occupation for which the necessary preliminary training is intellectual in character, involving knowledge, and to some extent learning, as distinguished from mere skill.

"*Second*, it is an occupation which is pursued largely for others and not merely for one's self.

"*Third*, it is an occupation in which the amount of financial return is not the accepted measure of success."




**View of the Education Display, and the story of the evolution of Materia Medica during the past hundred years.—Pharmacy Exhibit, Chicago World's Fair.**

## ASSAY OF GLYCERITE OF BISMUTH.*

BY JOSEPH L. MAYER.

The National Formulary on page 109 gives the following method for the assay of Glycerite of Bismuth:

"Dilute 5 cc. of Glycerite of Bismuth, accurately measured, with 100 cc. of distilled water, in a flask, add two drops of hydrochloric acid and pass a current of hydrogen sulphide through the solution until it is saturated. Allow the precipitate to settle and decant the supernatant liquid (which should be clear and colorless) through a Gooch crucible or filter, retaining the precipitate in the flask. Wash the precipitate a few times by decantation, then transfer it completely to the filter and wash with water until the washings give no test for chloride. Now wash twice with alcohol, then with warm carbon tetrachloride and again with alcohol. Dry at 100° C. and weigh. The weight of bismuth sulphide multiplied by 0.903 represents its equivalent in $Bi_2O_3$."

To avoid the use of hydrogen sulphide and the involved manipulation of this assay I have for a considerable number of years employed the following method for the quantitative determination of bismuth in glycerite of bismuth:

Accurately measure 5 cc. of Glycerite of Bismuth into a 400-cc. beaker, add about 100 cc. of water, heat to boiling, then add concentrated HCl until the precipitate which at first forms redissolves and then add ammonia water until a turbidity is produced, after which sufficient concentrated HCl is added to clear up the turbidity, to this boiling solution add an excess (about 50 cc. should be sufficient) of ten per cent ammonium phosphate solution, drop by drop from a 50-cc. pipette. Allow to settle and filter the precipitate on a Gooch crucible and wash with hot water until free from chlorides and after drying crucible and contents, place in a nickel crucible and heat until the weight is constant.

Multiply the weight of the precipitate by 0.7663 and then by 20, the result will be the grams of $Bi_2O_3$ in 100 cc. of sample.

The method is accurate, rapid, easily carried out and has everything to commend it.

RESEARCH AND ANALYTICAL LABORATORY,
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NEW YORK, N. Y.

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## DETERMINATION OF SPECIFIC GRAVITY OF PARAFFIN.†

BY BERL S. ALSTODT.

The U. S. P. under *Paraffinum* says the specific gravity is about 0.900 at 25° C., but specifies no method for its determination.

Under *Cera Flava* the U. S. P. not only states the range of specific gravity, but also provides a definite method for its determination. Under Cetaceum the Pharmacopœia states the range of specific gravity as 0.938 to 0.944 at 25° C. when determined by the method given under *Cera Flava* using alcohol warmed to from 38° to 40° C.

In view of the foregoing, I determined the specific gravity of paraffin by the procedure recommended under *Cera Flava*, modifying the method by using alcohol warmed to from 42° to 45° C. For comparison I made several experiments to

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* Read before the New York Pharmaceutical Association meeting, June 1933.
† New York State Pharmaceutical Association, 1933.

determine how this method and the commonly referred to "sinker method" agreed. The results checked very closely:

| | |
|---|---|
| Sp. Gr. by the method under wax [using alcohol warmed to from 42° to 45° C.] | 0.889 |
| Sp. Gr. by the "sinker method" | 0.888 |

Acting upon the suggestion of Dr. Joseph L. Mayer, I prepared mixtures of alcohol and water with their specific gravities accurately determined at 25° C. by means of a Geissler pycnometer. The range of specific gravities of these mixtures varies from the specific gravity of paraffin to that of wax.

With the samples of alcohol and water ready it is only necessary to place them in small test-tubes, adjust to a temperature of 25° C., add a globule to the contents of the tube and when the one is found in which the globule floats indifferently, read the specific gravity of the liquid from the label on the bottle and this represents the specific gravity of the substance examined.

SUMMARY.

1. The U. S. P. should describe a method for determining the specific gravity of paraffin.

2. The method for determining the specific gravity of wax modified, however, to have the alcohol warmed to from 42° to 45° C. is an excellent one for paraffin.

3. The results by the U. S. P. method for wax and the "sinker method" agree very well when applied to paraffin.

DEPARTMENT OF CHEMISTRY,
BROOKLYN COLLEGE OF PHARMACY, LONG ISLAND UNIVERSITY.

Seventh Congress of Military Medicine and Pharmacy, Madrid, 1933.

Reference has been made in a preceding issue of the JOURNAL to the Congress of Military Medicine and Pharmacy. The illustration above is from *The Pharmaceutical Journal and Pharmacist* of June 17th, and data are also taken from the same publication. Dr. A. Madinaveitia y Taburo demonstrated the "Utilization of the Spectrograph for the Determination of the Structure of Organic Substances." Pharmacist-Major Dr. R. Fraguas Fernández demonstrated the preparation of granules, tablets, capsules, medicinal wines, liquors and syrups; automatic filling machines and liquids. Other contributions related to sterilization, making of ampuls, preparation of ointments, by Dr. Miguel Campoy, Dr. Pedro Calvo y Muñoz Torrero and others. A motor pharmacy was demonstrated by Pharmacist-Major Dr. Miguel Campoy Irigoyen.

# A STUDY OF VEHICLES FOR MEDICINES.*

BY BERNARD FANTUS, H. A. DYNIEWICZ AND J. M. DYNIEWICZ.

## 2. AROMATIC ELIXIRS.

If the question were put to a vote: "Which is the most delicious of all vehicles?" would not the Aromatic Elixir receive first place? That it is popular is evidenced by the fact that, in Prof. E. N. Gathercoal's Prescription Ingredient Survey, it scored a usage of 63.7 per 10,000 prescriptions. We, therefore, started this study with the proposition that the elixir itself is not susceptible to further improvement.

A good deal of dissatisfaction has been expressed about the difficulty and tediousness of clarification of the aromatic elixir, as prepared in accordance with the present formula of the Pharmacopœia. This dissatisfaction is strikingly demonstrated by the number of modifications of the formula that have of late been proposed, all of which deal with the sequence of mixing of the ingredients. To arrive at a rational conclusion regarding these, it seemed necessary to devise a brief method of notation, to make it possible for the eye and mind to contrast the various processes advocated.

The order of mixing the ingredients of the "Aromatic Elixir of U. S. P. X" is as follows: to the compound spirit of orange (abbreviated O.) add the alcohol (abbr. A.), to this is added the syrup (abbr. Sy.) in several portions and afterward the water (abbr. W.); and the turbid mixture is clarified by filtering (abbr. f.) through talcum (abbr. T.). We propose to represent this sequence by the following formula:

O. A. Sy. W. T. + f.

### LESSENING OF VISCOSITY TO LESSEN FILTRATION TIME.

One group of suggestions that has been advanced, in order to shorten the filtration time, has been to lessen the viscosity of the fluid to be clarified by using sucrose (abbr. Su.) instead of the syrup; and dissolving it or the syrup in the fluid *after* its clarification.

Thus, Professor Crockett suggests to mix all the ingredients, excepting the sugar, to filter until clear; and then to dissolve the sugar in the filtrate. His sequence might be expressed by the formula:

O. A. W. T. + f. + Su.

Silver (1) proposes the mixing of the compound spirit of orange with one-half the amount of alcohol and adding the water in several portions, then the talcum and filtering the cloudy fluid through a well-wetted filter, returning the filtrate until clear. Clarification can be accomplished in three-quarters of an hour. We shall call this Chapter I of Silver's process. Chapter II consists in mixing the syrup with the other half of the alcohol. This is then added in divided portions to the clear liquid, shaking after each addition. This process may be expressed by the formula:

O. $^1/_2$A. W. T. + f. + Sy. $^1/_2$A.

* From the Laboratory of Pharmacology at the College of Medicine of the University of Illinois and assisted by a grant of the AMERICAN PHARMACEUTICAL ASSOCIATION.

The most complicated modification of the preclarification methods before the addition of the syrup, is that proposed by Schifflet (2). Like Silver, he holds back some alcohol from the original oil mixture and he uses some of this reserved alcohol, in an attempt to wash the talcum free from the absorbed oil; and finally adds another portion of the reserved alcohol to the finished preparation, in order to clarify it of any turbidity that has been produced by the addition of the syrup. His sequence of mixture might be represented in the following manner:

O. T. (A. 1W. 2) + f. (A. 1W. 2) + Sy. + A.

It will be noted that Schifflet's method also consists of two chapters. Chapter I, in which the oil mixture is treated with hydro-alcoholic solvent in the presence of talcum and Chapter II, in which the syrup and the balance of the alcohol are added to the clarified preparation without either of these ever having had the chance to become saturated with the oil mixture.

## EVALUATION OF METHODS.

The methods proposed, may be criticized under 3 headings:

1. Unfilterable subdivision of the volatile oils.
2. The use of talcum.
3. Partial use of solvent.

1. The real difficulty in clarifying the aromatic elixir prepared by all the methods in which the oil mixture is dissolved in the alcohol, to which then the aqueous moiety is added in several portions, is the production of an almost colloidal subdivision of the oil particles, a subdivision so fine as to make it incapable of clarification by simple filtration. This is, of course, done with the hope of securing maximum oil saturation of the finished liquid.

2. To remove this almost colloidal turbidity, three per cent of talcum is added which, as Krantz and Carr (3) have pointed out, coagulates the oil particles by neutralizing their negative electric charge by an oppositely charged ion and then absorbs the coagulated particles on the surface of the insoluble filtering medium. It is obvious that, if the subdivision of the oil were not so fine as to have it filter-passing, the use of the talcum and with it the time consumed in filtration could be dispensed with. Indeed, the use of the talcum also affects the hydrogen-ion concentration of the elixirs prepared with it, for we find that the hydrogen-ion concentration of elixirs in which it has been used varies between 6.08 and 6.01, while the hydrogen-ion concentration of the elixirs prepared without talc ranges about a $p_H$ of 5.24.

That the use of the talcum is not only time-consuming, but that it is also wasteful of oil, is suggested by the investigation of Henry Burlage, who compares an elixir made by the official method with one made in the same way, but with the use of twice the quantity of talcum. He finds the percentage of oil content of the latter to be 0.0044+ as compared with the oil content of the official elixir at 0.19−, quite a difference.

3. Silver and Schifflet, by reserving a portion of the solvent (alcohol and syrup), to be added to the clarified oil-alcohol-water mixture (Chapters I and II of their processes) commit the error of not giving *all* the solvent a chance to become

saturated with oil. How grievous this error is, has been beautifully demonstrated by Burlage's investigation which showed that the elixir resulting from Schifflet's procedure contained only 0.003+ and that from Silver's procedure, in which even more alcohol is kept from saturation with the oils, contained only 0.001+ per cent of volatile oil.

### THE PRINCIPLES OF ELIXIR MAKING.

We may now be ready to formulate certain principles that might enable us to develop a more satisfactory formula.

1. *Viscosity must be kept low until after clarification.* With this principle most of the students of this question agree.

2. *Filtration through talcum* or other absorbent powder *must be abandoned*, because it wastes time and oil, and changes the hydrogen-ion concentration of the resulting elixir.

3. To abandon filtration through talcum, and yet be able to add an excess of oil mixture to secure complete oil saturation of the elixir, we must *avoid precipitation of the oils in globules so fine that they pass through filter paper*, which we can do by taking advantage of the law that the fineness of a precipitate is in proportion to the dilution of the reacting solutions. At the same time, the globules must be small enough to remain in suspension: for, to secure the same degree of oil solution from the coarser globules, we must allow a time factor to enter; and, unless some of the oil remains in suspension, frequent agitation would be required to give the solvent adequate opportunity at oil surfaces. No doubt, occasional agitation might be of value in any case, as some of the oil accumulates on the surface. We find that, if we add the compound spirit of orange to the mixed solvents—using an aliquot portion of water instead of the syrup—we secure exactly such subdivision of the oil.

That temperature affects the size of oil globules is shown by the following observations: when we add the compound spirit of orange to the mixed solvents heated to a temperature of 71° C. the resulting liquid is almost clear, but it becomes milky on cooling to room temperature, the degree of its cloudiness being somewhat greater than that of the mixture made at room temperatures. When we agitated the compound spirit of orange with the mixed solvents, previously cooled to a temperature of 10° C., we find that the resulting mixture is still less turbid and that there is a greater quantity of unemulsified oil floating on the surface. The clear filterability of the mixture secured at room temperature, when a hard filter is used, makes the artificial temperature changes merely of interest in showing that variable results might be obtained by variations in temperature.

4. Both Silver and Schifflet have demonstrated that it is a poor policy to retain any of the solvent until after clarification; because, of course, we cannot get a saturated solution unless we give all of the solvent a chance to become saturated.

### A RAPID METHOD OF ELIXIR PREPARATION.

It seems, then, that the problem of a more expeditious preparation of the official elixir would be solved were the very *fine* subdivision of the oils prevented: as can be done by adding the compound spirit of orange to *all* the solvent ingredients, previously mixed; permitting this mixture to stand for twenty-four hours

(if time permits), and filtering through a *hard* filter (Whatman 50) to absorb the excess of oil. This process is strictly analogous to the modern method of preparation of aromatic waters, which was introduced into the tenth revision of the Pharmacopœia to take the place of the talcum process, that was objected to, not only because of its adding foreign ions to the solution, but also because the finished water seemed less aromatic.

After all, one cannot force more solute into a liquid than that liquid *can* dissolve; and saturation will occur if one gives the solvent time enough to act upon the solute, even if the latter be not present in the finest possible degree of subdivision. Therefore, it seems to us an error to produce so fine a subdivision of the oil that one has great difficulty in filtering out the excess; and must add an absorbent to the liquid, which wastes not only time but also oil in filtration.

While we hesitate to make the existing confusion still more confounded by proposing another sequence to the many that have been advanced, we do so with the belief that we might thereby clarify the situation and the elixir as well.

**ELIXIR AROMATICUM.**

**Aromatic Elixir.**

| Elix. Arom. | Simple Elixir |
|---|---|
| **Compound Spirit of Orange** | **12 cc.** |
| **Sucrose** | **320 Gm.** |
| **Alcohol** | **250 cc.** |
| **Distilled Water** | **550 cc.** |
| To make | **1000 cc.** |

Mix the alcohol with the water, add the compound spirit of orange, and agitate vigorously; repeating the agitation from time to time in the course of twenty-four hours. Filter through a hard filter (such as Whatman 50) returning, if necessary, the first portions of the filtrate until it passes through clear. Dissolve the sucrose in the clear filtrate, either by agitation or by percolation, adding enough of water and alcohol, in the proportion of 2 of water to 1 of alcohol, to make the final product measure 1000 cc.

This gives us as the mixing formula:

A. W. O. + f. + Su.,

which may seem almost too simple. Our forefathers said: "*Simplex sigillum veri.*" (The simple is the sign of the truth.)

(*"Iso-Alcoholic Elixirs" follow in next issue of the* JOURNAL.)

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STERILITY OF ALCOHOL.

H. Eschenbrenner, *Apoth.-Ztg.*, 47 (1932), 1578. The examination of 34 samples of alcohol of strengths ranging from 70 per cent upward showed that 20 of these were not sterile. In alcohol taken from storage tanks, and especially in the sediment from the tanks, a great variety of spore-forming bacteria were found, chiefly from the groups of hay bacilli, *B. subtilis* and at least five kinds of gram-positive rods. Tetanus spores could not be detected. Although definitely pathogenic bacteria have never been found in alcohol, it is not certain that these other forms are entirely innocuous. It is thus necessary to sterilize alcohol which is to be used for surgical purposes or for the sterilization of instruments, either by distillation or by passing it through a sterilizing filter.

# THE DEPARTMENT OF THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

C. B. JORDAN—CHAIRMAN OF EXECUTIVE COMMITTEE, A. A. C. P., EDITOR OF THIS DEPARTMENT.

## AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY.

### THIRTY-FOURTH ANNUAL MEETING.

**Officers:** *President*, Charles H. Stocking; *Vice-President*, Robert C. Wilson; *Chairman of Executive Committee*, Charles B. Jordan; *Secretary-Treasurer*, Zada M. Cooper.

**Monday, August 28th.**

9:00 A.M. Meeting of Executive Committee.
9:30 A.M. Meetings of Teachers' Conferences.
**Pharmacy,** Louis W. Rising, *Chairman.*
**Chemistry,** Perry A. Foote, *Chairman.*
**Pharmacognosy and Pharmacology,** B. V. Christensen, *Chairman.*
**Pharmaceutical Economics,** W. Bruce Philip, *Chairman.*

### CONFERENCE OF TEACHERS OF PHARMACY.

**Officers:** *Chairman*, Louis W. Rising; *Vice-Chairman*, Henry M. Burlage; *Secretary*, Frederick V. Lofgren.

### PROGRAM.

"The Necessity for Increasing Emphasis on the N. F. in Pharmacy Courses," William J. Husa.

"When Dispensing Should Begin in the Four-Year Course and How Much Time Should Be Devoted to It." D. B. R. Johnson.

"The Part That Purdue School of Pharmacy Plays in the Student Health Service of the University," H. W. Heine.

"The Teaching of Incompatibilities," W. G. Crockett.

"How Should a Course in Incompatibilities Be Taught and How Much Time Should Be Devoted to It?" D. B. R. Johnson.

"Teaching Incompatibilities," John S. Mitchell.

"The Teaching of Incompatibilities," H. A. Langenhan.

"What Type and Amount of Work Should Be Given a Student on Manufacturing Special Preparations for the Dental Profession?" A. O. Mickelsen.

"Shall Pharmacy Colleges Teach Dental Pharmacy?" George C. Schicks.

### CONFERENCE OF TEACHERS OF CHEMISTRY.

**Officers:** *Chairman*, Perry A. Foote; *Secretary*, Hugh C. Muldoon.

### PROGRAM.

"What the Department of Pharmacy Expects of the Department of Chemistry," H. C. Newton; discussed by H. V. Arny.

"The Inter-Relation of the Departments of Pharmacognosy-Pharmacology and Chemistry," B. V. Christensen; discussed by W. O. Richtmann.

"Why Organic Chemistry Should Be Taught in the School of Pharmacy," C. J. Klemme; discussed by Ernest Little.

### CONFERENCE OF TEACHERS OF PHARMACOGNOSY AND PHARMACOLOGY.

**Officers:** *Chairman*, B. V. Christensen; *Secretary*, Charles E. F. Mollett.

PROGRAM.

(*To be supplied.*)

CONFERENCE OF TEACHERS OF PHARMACEUTICAL ECONOMICS.

**Officers:** *Chairman*, W. Bruce Philip; *Secretary*, Florin J. Amrhein.

PROGRAM.

(*To be supplied.*)

**Monday, August 28th, 2:00 P.M.**

First Session of the Association.

Roll Call.
Memorial to W. A. Puckner, L. E. Warren.
Appointment of Committee on Resolutions.
Address of the President, Charles H. Stocking.
Report of the Secretary-Treasurer, Zada M. Cooper.
Report of the Executive Committee, Charles B. Jordan.
Appointment of Nominating and Auditing Committees.
Paper—"Introductory Lecture to a Course in History of Pharmacy," Edward Kremers.
Reports of Standing Committees:

Committee on Higher Educational Standards, William J. Husa.
Committee on Curriculum and Teaching Methods, Wortley F. Rudd.
Committee on Activities of Students and Alumni, Adley B. Nichols.
Delegates to American Council on Education, Rufus A. Lyman.
Committee on Relation of Boards and Colleges, Arthur F. Schlichting.
Syllabus Committee, J. G. Beard.

**Monday, August 28th, 6:00 P.M.**

Annual Dinner.
Address, Dr. Glen Frank, President of the University of Wisconsin.

**Monday, August 28th, 8:00 P.M.**

Second Session of the Association.

Report on "Proposed Standards for the Classification of Schools of Pharmacy," A. G. DuMez.
Report of Committee on Membership Standards, Ernest Little.

**Tuesday, August 29th, 2:00 P.M.**

Third Session of the Association.

Reports of Special Committees:

Committee on Student Branches of the AMERICAN PHARMACEUTICAL ASSOCIATION, B. V. Christensen.
Committee on Establishment of a Pharmaceutical Corps in the United States Army, Townes R. Leigh.
Committee on the Study of Pharmacy, Charles B. Jordan.
Committee to Confer with Executive Council of the Association of American Medical Colleges, Charles B. Jordan.

Paper—"Use of the Library in Undergraduate Instruction," Charles O. Lee.
Reports of Special Representatives:

Representatives on American Council on Pharmaceutical Education, A. G. DuMez.
Representative to Drug Trade Bureau of Public Information, William G. Crockett.
Reporter on Biological Abstracts, Heber W. Youngken.
Representatives to National Conference on Pharmaceutical Research, Glenn L. Jenkins.

Representatives to the Druggists' Research Bureau, Paul C. Olsen.
Representatives to the National Drug Trade Conference, A. G. DuMez.
Representative to the National Association of Retail Druggists, Theodore J. Bradley.
Historian, Edward Kremers.
Representative on Committee on Centennial Celebration, William B. Day.
Representative on National Drug Store Survey Committee, Charles E. Caspari.
Representative to the Annual Congress on Medical Education and Licensure, Charles B. Jordan.

Unfinished Business.
Miscellaneous Business.
Election of Officers.
New Business.
Executive Session.

JOINT SESSION OF THE NATIONAL ASSOCIATION OF BOARDS OF PHARMACY AND THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY.

**Tuesday, August 29th.**

Report of the Fairchild Scholarship Committee, E. G. Eberle, *Chairman*.

Paper—"Is Compulsory Apprenticeship Registration Working a Hardship on Young Men Entering Pharmacy?" Charles B. Jordan.

Resolutions from District Meetings, A. F. Schlichting, A. C. Taylor.

*Corrections and additions will be made in Official Program.*

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## PRESENTATION OF PRESIDENTIAL CHAIR TO PHARMACEUTICAL SOCIETY OF GREAT BRITAIN.

Secretary H. N. Linstead, of the Pharmaceutical Society of Great Britain, in conjunction with the Executive of the Australian and New Zealand Pharmaceutical Association, completed arrangements during the month for a special broadcasting ceremony to be associated with the presentation of the Presidential chair to the Society by the combined pharmaceutical organizations of Australia and New Zealand.

To fittingly mark the occasion the chair is to be presented at the 70th annual meeting of the British Pharmaceutical Conference, to be held in London during the last week in July. A representative of the British government will be present, and it is expected that about 700 pharmacists will attend the banquet.

The arrangements comprise the utilization of the London-Sydney telephone service to broadcast the ceremony. The officials of the Australian Association will be in attendance at Sidney headquarters at 3 A.M. on the night of the presentation, when the interchange of speeches will take place. Mr. David Dunn, president of the Australian and New Zealand Association, will formally present the chair, and the other executive officers will take part in the proceedings. Amplifiers will be installed in the Conference Hall in London, so that all of those present will be able to listen to the addresses.

## THE JAPAN PHARMACEUTICAL SOCIETY.

Participated in by some 2000 delegates assembled from all parts of Japan, the 53rd general meeting of the Japan Pharmaceutical Society was held at the Gakushikai Hall, Kanda, Tokyo. The meeting was presided over by President Ueno. The officers are:

*President*, Dr. Kotaro Nishizaki, former head of the Imperial Hygienic Laboratory in Tokyo; *Vice-President*, Dr. Sentaro Tanii; *Directors*, Dr. Pharmacist-Lieutenant-General Mataji Watanabe, Professor Katsuznemon Keimatsu of the Tokyo Imperial University, Professor Heizaburo Kondo and Professor Yasuhiko Asahina of the same university.

Reports on the results of various researches and special lectures were delivered. The following are the more important of the reports made at the meeting: Seikichi Nakamura on "Shinabana;" Shukan Suzuki and Ichiro Keimatsu on "A Comparative Study of Various Aspirins;" Dr. Akira Ogata of the Tokyo Imperial University on "A Study of Male Hormone and on "A Study of Testicular Hormone;" Ryutaro Ueda (Tokyo) on "The Experimentary Cultivation of Artemisia Cinæ;" Shinjiro Aoyama of the Imperial Hygienic Laboratory on "The Manufacture of Phenacetin;" Prof. Katsuzaemon Keimatsu on "A Synthetic Study of Selen Organic Compounds."

# ASSOCIATION BUSINESS

## AD INTERIM BUSINESS OF THE COUNCIL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, 1932–1933.

Office of the Secretary, 10 West Chase St., Baltimore, Md.

LETTER NO. 9.

June 20, 1933.

*To the Members of the Council:*

*65. Tentative General Program for the Eighty-First Annual Meeting.* With the approval of President Philip, Local Secretary Stanley, and the Committee on Standard Program of the Council, the Secretary submits the following tentative general program. Officials of the various affiliated organizations represented in the program have approved those features in which their respective organizations are directly interested.

GENERAL PROGRAM FOR THE EIGHTY-FIRST ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION AND RELATED ORGANIZATIONS, HOTEL LORAINE, MADISON, WISCONSIN, AUGUST 22–SEPTEMBER 2, 1933.

All dates included in special fare arrangements with railroads.

AUGUST 21–25.

Plant Science Seminar. Program and Meeting Rooms to be arranged.

SATURDAY, AUGUST 26.

Afternoon and Evening.

National Conference on Pharmaceutical Research—Colonial Room.

American Council on Pharmaceutical Education—Time and Place to be arranged.

MONDAY, AUGUST 28.

9:00 A.M. Council A. PH. A.—Green Room.
9:00 A.M. N. A. B. P.—Pompeian Room.
9:00 A.M. A. A. C. P.—Executive Committee—Room 201.
Chemistry Conference—Crystal Room A.
Pharmacy Conference—Crystal Room B.
Materia Medica Conference—Colonial Room.
Pharmaceutical Economics Conference—Senatorial Room.
1:30 P.M. N. A. B. P.—Pompeian Room.
1:30 P.M. A. A. C. P.—Crystal Room.
6:00 P.M. Dinner N. A. B. P.—Pompeian Room.
6:00 P.M. Dinner, A. A. C. P.—Crystal Room.
9:30 P.M. Reception—(Informal) followed by dancing—Crystal Room.

TUESDAY, AUGUST 29.

9:00 A.M. Joint Meeting N. A. B. P. and A. A. C. P.—Crystal Room.
1:30 P.M. First Session, House of Delegates—Crystal Room.
2:30 P.M. N. A. B. P.—Pompeian Room.
2:30 P.M. A. A. C. P.—Crystal Room.
6:30 P.M. Banquet, A. PH. A. and Related Organizations—Crystal Room.

WEDNESDAY, AUGUST 30.

9:00 A.M. First General Session, A. PH. A.—Crystal Room.
12:15 P.M. Luncheon, Syllabus Committee—Senatorial Room.
2:00 P.M. First Session, Scientific Section—Crystal Room A.
2:00 P.M. First Session, Section on Education and Legislation—Crystal Room B.
2:00 P.M. First Session, Section on Commercial Interests—Pompeian Room.
2:00 P.M. First Session, Conference of Pharmaceutical Association Secretaries—Colonial Room.
3:00 P.M. Joint Meeting, Executive Committee, N. A. R. D. and Council A. PH. A.—Green Room.
6:00 P.M. Dinner, Kappa Psi Fraternity.
6:00 P.M. Dinner, Phi Delta Chi Fraternity.
6:00 P.M. Dinner, Rho Chi Fraternity, followed by annual convention.
6:00 P.M. Dinner, Lambda Kappa Sigma Sorority.
6:00 P.M. Dinner, Kappa Epsilon Fraternity.
8:00 P.M. Second Session, House of Delegates—Crystal Room.

THURSDAY, AUGUST 31.

9:00 A.M. Council A. PH. A.—Green Room.
9:00 A.M. Second Session, Section on Commercial Interests—Pompeian Room.
9:00 A.M. Second Session, Scientific Section—Crystal Room A.
9:00 A.M. First Session, Section on Practical Pharmacy—Crystal Room B.
9:00 A.M. First Session, Section on Historical Pharmacy—Senatorial Room.
9:00 A.M. First Session, Conference of Law Enforcement Officials—Colonial Room.
12:00 M. Veteran Druggists' Luncheon—Main Dining Room.
2:00 P.M. Second General Session, A. PH. A.—Crystal Room.
5:30 P.M. Lawn Party and Dinner at the Home of Dr. Edward Kremers. (Busses will leave the Hotel Loraine at 5:00 to 5:15 P.M. and will return before 8 P.M. for the evening sessions.)
8:00 P.M. Joint Session, Scientific Section and Section on Practical Pharmacy and Dispensing—Crystal Room.
8:00 P.M. Joint Session, Section on Education and Legislation, Conference of Pharmaceutical Law Enforcement Officials and Conference of Pharmaceutical Association Secretaries—Pompeian Room.

FRIDAY, SEPTEMBER 1.

9:00 A.M. Third Session House of Delegates—Crystal Room.
2:00 P.M. Third Session, Scientific Section—Crystal Room A.
2:00 P.M. Second Session, Section on Practical Pharmacy—Crystal Room B.
2:00 P.M. Second Session, Section on Historical Pharmacy—Senatorial Room.
2:00 P.M. Second Session, Conference of Law Enforcement Officials—Colonial Room.
2:00 P.M. Second Session, Conference of Pharmaceutical Association Secretaries—Pompeian Room.
5:45 P.M. Dinner, Former Presidents A. PH. A.—Colonial Room.
6:00 P.M. Special dinners.
7:30 P.M. Final Session, House of Delegates—Crystal Room.
8:30 P.M. Final General Session A. PH. A.—Crystal Room.
9:30 P.M. Farewell Party—Crystal Room.
10:00 P.M. Council A. PH. A.—Green Room.

SATURDAY, SEPTEMBER 2.

All-Day Entertainment to be arranged.

TRANSPORTATION TO MADISON.

On account of the Century of Progress Exposition, greatly reduced rates to Chicago will be in effect from most places—as low as one fare plus 25 cents for the round trip and slightly higher rates for longer time limits.

The Committee on Transportation has secured a reduced round-trip rate of one and one-third fare to Madison on the identification certificate plan good for thirty days and the certificates will be sent to members later. Tickets on this plan will be on sale as early as August 14th in distant territories.

It is suggested: (1) That members should buy the best special excursion ticket to Chicago they can get and use the identification certificate to buy round-trip ticket from Chicago to Madison; (2) members whose route to Chicago is through Madison should buy the best special excursion ticket to Chicago and obtain stop-over at Madison for the meeting.

(*Motion No. 20*) *It is moved by Kelly that the tentative General Program of the Eighty-First Annual Meeting be approved.*

66. *Authorizing Dr. Hilton to Sign Checks in the Absence of Treasurer Holton.* Treasurer Holton expects to be away during the months of July and August and requests that Dr. S. L. Hilton be given authority to sign ASSOCIATION checks during his absence. Dr. Hilton has kindly consented to act and the necessary forms have been furnished by the Merchants and Newark Trust Company and by the Baltimore Trust Company.

(*Motion No. 21*) *It is moved by Eberle that S. L. Hilton be given authority to sign Association checks during the absence of Treasurer Holton, and that the president and secretary be authorized to execute the necessary papers to be filed with the approved banks of deposit.*

67. *Research Award.* Chairman Arny of the Committee on Research writes:

"Ten voting sheets have come back in response to Research Committee Bulletin No. 3. All favor granting $1000 from the Research Fund to Dr. W. J. Husa and his associates at the University of Florida for a continuance of his fine work on Extraction.

"Dr. Husa writes me that it will be a great service to him if he can be officially informed of the grant as quickly as possible. As I understand his letter, the check itself may follow our usual procedure of a September dating. On the other hand, official notification of the ASSOCIATION'S action will greatly facilitate his arrangements with his University as to research staff appointments, as said appointments should be made on July first."

(*Motion No. 22*) *It is moved by Arny that a grant of $1000 from the Research Fund be made to Dr. W. J. Husa for the continuation during 1933–1934 of his research on extraction, payment to be made after the Madison meeting.*

*68. Contract for Printing, Binding and Distributing the Year Book Volumes 20 and 21, for 1931 and 1932.* Volume 19 of the YEAR BOOK, for 1930, has recently been completed and distributed. Editor DuMez recently advised that copy for Volume 20, for 1931, is completed and that copy for Volume 21, for 1932, will be completed in about four months, and recommended that they be issued in one binding, because of the saving, as was done with Volumes 16 and 17. Under this arrangement it is possible that the combined volume will be distributed toward the end of this year bringing the publication up-to-date.

Bids were promptly obtained for the combined volumes from the firms that have recently submitted bids on the publication. The Lord Baltimore Press, which firm has printed and distributed the last four volumes, submitted the lowest bid. The prices are the same as for Volume 19, with the exception of proportionate increases for the added binding and shipping on account of the combined volume, as the firm was able to protect against recent advances in the cost of materials.

The Treasurer's Reports and the Reports of the Progress of Pharmacy for 1931 and 1932 will be printed separately in the double volume and the index will be combined, following the arrangement for Volumes 16 and 17.

The larger reading page used in printing the Report of the Progress of Pharmacy in Volume 19 will probably be used throughout Volumes 20 and 21 as it effected considerable saving in cost and will reduce the size of the double volume.

(*Motion No. 23*) *It is moved by DuMez that Volumes 20 and 21 of the Year Book be issued in one binding, and that the contract for printing, binding and distributing the combined book be awarded to the Lord Baltimore Press, Baltimore, Md., on the basis of their bid of June 17, 1933.*

*69. Applicants for Membership.* The following applications properly endorsed and accompanied by the first year's dues have been received:

No. 161, George Edwin Byers, 1808 Spring Garden St., Philadelphia, Pa.; No. 162, Charles C. Charmley, 902 E. Johnson St., Madison, Wis.; No. 163, James M. Dille, 4311 Grant St., Omaha, Nebr.; No. 164, Miles Edward Drake, 6123—83rd St., S. E., Portland, Oreg.; No. 165, Joseph Hamilton Edwards, Cayon & New Sts., Basseterre, St. Kitts, B. W. I.; No. 166, Frank Eten, 299 Stuyvesant Ave., Lyndhurst, N. J.; No. 167, Inez Gilbert, 521 S. 11th St., Corvallis, Oreg.; No. 168, Joseph Matkowitz, 179 Dumont Ave., Brooklyn, N. Y.; No. 169, Tom Matthews, 2429 East 17th Ave., Spokane, Wash.; No. 170, Israel Jacob Rechtweg, 304 Echo Place, Bronx, N. Y.; No. 171, T. H. Rider, c/o Wm. S. Merrell Co., Cincinnati, Ohio; No. 172, Abe A. Rovell, 5802 Tower Ave., Superior, Wis.; No. 173, Ernest Royce, Napa State Hospital, Imola, Calif.

(*Motion No. 24*) *Vote on applications for membership in the American Pharmaceutical Association.*

E. F. KELLY, *Secretary.*

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## THE NEW DANISH PHARMACOPŒIA.

The eighth edition of the Danish Pharmacopœia was issued in March. A decided change is the adoption of the International Chemical Nomenclature which is in accord with that of the United States Pharmacopœia. Nearly all the tests and assays are defined in connection with the drugs and preparations. Biological assay is prescribed for digitalis and for cod liver oil.

# COMMITTEE REPORTS

## THE PHARMACEUTICAL ASPECTS OF SOCIALIZED MEDICINE.

BY H. V. ARNY, PH.D.*

On January 9, 1933, at the mid-winter session of the general committees of the N. Y. S. Ph. A. President Miller appointed as a special committee on socialized medicine Messrs. Goldschmidt, Gesoalde, Seley and Arny. During the winter this committee held two conferences and transacted other business by correspondence. A final conference was held at Stamford, N. Y., on June 20th, and the following report represents the unanimous opinion of the committee after six months' study of the important and complicated problem.

The main task of the committee was a study of the now famous "Final Report of the Committee on the Costs of Medical Care." Explanatory and critical literature from medical and pharmaceutical journals and from the press has been scanned. Of importance, second only to the "Final Report" is the book "Medicinal Education," a report emanating from the Commission on Medical Education. From the mass of detail this afforded us, your committee has elicited the following facts.

### REPORT OF COMMITTEE ON COST OF MEDICAL CARE.

This committee consisted of 50 members, medical workers, social workers, educators and business men. There were 15 practicing physicians, 2 dental surgeons and one practicing pharmacist (Mr. Ambrose Hunsberger of Philadelphia). The statistical work was conducted by a research staff of 13 experts, one of whom (Dr. Robert P. Fischelis of Trenton) is a pharmacist. The survey covered a period of five years and resulted in the publication of a number of statistical Bulletins and a "Final Report" which contains the "Majority Recommendations" (five in number). It also contains two minority reports, as well as a number of printed expressions of individual opinions. These recommendations and minority reports have been given publicity in the pharmaceutical press, hence at this time we will merely outline the committee recommendations (signed by all but 13 members of the committee) and the recommendations of the principal minority group. It is significant that this minority report is signed by 8 practicing physicians and one layman.

*The Majority Recommendations* may be condensed to the following excerpt, but it is only fair to us to urge that those interested read the full text of the recommendations as found on page XVI of the "Final Report" of the Committee.

1. Medical service should be furnished largely by organized groups: physicians, dentists, nurses, pharmacists, etc.
2. Recommendation that all basic public health services be extended so as to become available to the entire population.
3. Recommendation that the costs of medical care be placed upon a group payment basis: through insurance, through taxation or through both of these methods.
4. Recommendation that there be formed agencies (state and local) for the study, evaluation and coördination of medical service.
5. Recommendations as to improvements in professional education: of physicians, of dentists, of pharmacists, of nurses and nursing aids and of midwives. As to pharmacists, the education should "place more stress on the pharmacist's responsibilities and opportunities for public service."

*The Principal Minority Report* stresses the following:

1. Governmental competition in the practice of medicine should be discontinued and its activities should be restricted to the medical departments of the Army, Navy and other governmental agencies and to the various types of government hospitals.

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* A report of the committee on socialized medicine of the New York State Pharmaceutical Association, presented to the Association at its 1933 meeting.

2. The Government should relieve the private practice of medicine from the care of indigents.

3. Approval of Item No. 4 of the Majority Report.

4. Restoration of the general practitioner to the central position in medical practice.

5. Recommendation that the corporate practice of medicine financed through intermediary agencies be vigorously opposed.

6. Recommends the trial of methods which can be rightly fitted into present-day practice without interfering with the fundamentals of medical practice.

7. Recommends the development by state and county medical associations of plans for medical care.

REPORT OF THE COMMISSION ON MEDICAL EDUCATION.

The book "Medical Education" prepared by this Commission under the leadership of Dean Rappleye of Columbia University School of Medicine discusses the education of physicians rather than socialized medicine. These two subjects are, however, so closely intertwined in present-day medical thought that much valuable information concerning the present trends of the practice of medicine are given. Of particular value are the 120 statistical tables giving present (1932) information concerning all phases of the practice of medicine. As the book came out at about the same time as the "Final Report" of the Committee on the Costs of Medical Care, the information given in one book supplements the other, while opinions upon the same subject as present in the two books sometimes exhibit marked differences. The book "Medical Education" is essentially a presentation of statistical information. Recommendations are few and informative. Some of these are summarized below:

1. Deplores self-medication, stating that this is "largely through patent medicines and home remedies supplied by the 60,000 drug stores of the country."

2. Aides used by the medical practitioner are (*a*) hospitals, (*b*) clinics, (*c*) nurses, (*d*) dentists, (*e*) optometrists, (*f*) midwives, (*g*) laboratory services, (*h*) dietetics. It is significant that nowhere in the list is pharmacy mentioned. It is further significant that the words "pharmacy," "drug" and "medicines" are not to be found in the index of the book.

3. Too much rigidity is demanded by law in the medical school curriculum.

4. Criticizes pharmacology courses for clinging "to the older type of teaching, including identification of drugs, compounding of prescriptions and other features of pharmacy."

5. Discussing therapeutics, the book states "there is less reliance placed now upon drug therapy than was the case in the past because the virtues claimed for many drugs have not as yet been demonstrated." Modern therapeutics emphasizes organ-therapy, vaccines, sera, radium, heliotherapy, etc.

6. Pharmacology teachers should emphasize the part played by patent medicines and nostrums in directing the public to medication without diagnosis.

THE RELATION OF PHARMACY TO THESE REPORTS.

As citizens, we are all deeply interested in problems relating to medical care. As members of the pharmaceutical calling, we have a sympathetic interest in the well-being of that fine group of professional men, the medical practitioners. As members of the N. Y. S. Ph. A., our retail pharmacists must ask the question, "Where do we fit in the plans outlined in the two reports outlined above?"

*In the Rappleye Report*, Pharmacy is treated with contemptuous neglect. This report is a typical example of the therapeutic nihilism that has pervaded the minds of the medical teachers during the past quarter-century; a situation that may be condensed to the aphorism: diagnosis everything, treatment nothing. Medical students of to-day are trained to accurately diagnose a disease and are then left to flounder as far as treatment is concerned. This floundering finally lands the young physician into the arms of the "ethical private formula" manufacturer and thus is started the prescribing of proprietaries and the self-medication on the part of the public which medical publicists so deeply deplore.

There is, in truth, no message of hope for Pharmacy in the Rappleye Report.

*In the Bulletins of the Committee on Cost of Medical Care*, there is much material for study by us pharmacists. The book, "The Costs of Medicines," by Drs. C. Rufus Rorem and Robert P. Fischelis (*Bulletin No. 14*) should be read by every retail druggist, since it gives us information, statistical and otherwise, concerning the present condition and trends of retail pharmacy that few of us have realized. It seems to your committee quite unfortunate that so little of the material in Dr. Fischelis' book was utilized by the medical care committee in its Majority Report.

This Majority Report considers Pharmacy from two angles. One is in the shape of the year-long propaganda of the American Medical Association against proprietary medicines. In our reading of this portion of the Majority Report, your committee fails to note mention of one of the primal causes of the "nostrum evil" of to-day, the evolution of which may be traced through the following steps: (*a*) therapeutic nihilism in medical schools, (*b*) ignorance of young physicians as to rational prescribing, (*c*) recourse to the manufacturers of "ethical proprietaries," (*d*) the "ethical proprietary" of to-day becomes the advertised "nostrum" of to-morrow; at times, with the printed boast "prescribed by 50,000 physicians."

As to the pharmacy in which we are interested, the prescription business of our retail pharmacies, the Majority Report gives us cold comfort. The frank recommendation of the majority of the medical care committee is that medical practice of the future be concentrated in medical centers or in private group clinics. We pharmacists know what step-motherly treatment the average hospital pharmacist receives from his medical superiors. We know that in most hospital groups "low pharmaceutical salaries" and "cheap drug supplies" are the slogans. One of us has personal knowledge of one of the best hospitals in a large western city, where the gifted pharmacist and his staff are tucked away in the dark basement next to the hospital kitchen. This situation is evidently designed to emphasize the statement of Sir Thomas Bulleyn (16th Century) that the apothecary is the physician's cook. If the proposed medical plans of the "Majority Report" go through; if all of the 120,000,000 people in the United States have to go to hospitals and private clinics for medical treatment; if the independent medical practitioner is to go to the wall, then the independent pharmacist is doomed to extinction.

Of course, the extremists of the medical care committee are not to have their way. We have already mentioned that the principal minority report of the medical care committee is signed by eight out of the fifteen practicing physicians on the committee and discussions during 1933 at state and local medical society meetings indicate a vigorous opposition on the part of the rank and file of medical men in general practice against such socialistic propositions.

This fight should be waged upon the basic proposition: shall the individual practitioner be destroyed for the aggrandizement of the few, who shout the battle cry "For the Public Good?" It is obvious to us that this battle will be fought by the individual medical practitioner and that we pharmacists need not worry as to the outcome; at least for fifty years to come.

Where, then, does Pharmacy come in? In our opinion, in the comparatively near future pressure will be brought to bear by the groups interested in this "Cost of Medical Care" movement to limit the practice of pharmacy more and more to the compounding of prescriptions and to the sale of drugs, medicines and poisons. All of us have given voice to this program as the aim of ideal Pharmacy. The cold facts as presented in the Fischelis Bulletin and extracted from other sources of information indicate that all of the prescriptions written by the physicians of the United States (165,000,000 prescriptions) distributed among all of the drug stores of this country (60,000) means 2780 prescriptions per annum, or 8 per day per drug store. This means 4 prescriptions per day per registered pharmacist. Other statistical data indicate that hasty, thoughtless and speedy legislation of restrictive character would tend to put 80 per cent of our drug stores out of business.

Your committee is ready to concede that pharmacy is overcrowded, but in these days all callings are overcrowded. Significant is one of the tables presented in the Rappleye Report. It will be recalled that the avowed object of the greatly increased requirements set for admission into medical schools in or around 1910 was to stop overcrowding in the medical profession. The Rappleye statistics show that between 1906 and 1920 the number of medical graduates in the United States dropped from 5364 to 3047 and that from 1920 to 1932 the graduate figure increased from 3047 to 4936. This is of course far more than the percentage increase in population. It is of great interest to note that during the past five years while the highly restricted medical courses

have produced an almost 60 per cent increase in medical graduates, the less restricted pharmacy courses have produced a decrease in graduates approximating 40 per cent.

### A PROGRAM FOR PHARMACY.

What can Pharmacy and this Association do to meet this very serious issue? Your committee offers the following suggestions:

*1. Pursue a "Laissez faire" Policy.*—This would be suicidal. The pharmacist of the Province of Ontario overlooked the passage in 1932 of certain "medical relief regulations" by the legislative device known in Canada as "Order-in-Council" and awoke to find that this legislation included a health insurance clause providing that physicians furnish for appropriate compensation not only medical services but also necessary medical supplies. A deputation from the Ontario Retail Druggists' Association called upon the Minister of Public Works and Labor, Dr. Monteith, who was unmoved by the plea of the druggists that "the necessary medical supplies" should be furnished by pharmacists. As the *Canadian Pharmaceutical Journal* puts it:

> The medical relief regulations were drawn up without the slightest regard for the retail druggists.
>
> They have been left out of the picture entirely.

*2. Join Physicians and Dentists in Fighting the Proposed Plans.*—Two warnings should be sounded in this connection. The three branches of medical service; the physician, the dentist and the pharmacist; must be careful in planning their line of attack. In the first place, among those of the medical costs committee who back the "Majority Report" are included a number of outstanding laymen distinguished for their altruistic interest in philanthropy and social service. Before legislative committees, members of this group command respectful attention because of the past records of disinterested social service. Their arguments that the proposed legislation is intended for the general good of the vast group of inarticulate poor, will be hard to meet. To oppose these arguments by tearful tales of doctors, dentists and druggists who will be reduced to penury, true though it may be, will scarcely serve the need of vigorous opposition. The following remarks on the subject made to medical men by Dr. Lewellus F. Barker of Johns Hopkins University are significant:

> I want to warn my colleagues in the profession against too negative an attitude. This world is not static. This world is changing all the time. The medical profession must change with the rest of the world and keep pace with it. The negative attitude of our English and German *confrères* was very disastrous to the medical profession. That negative attitude did not prevent the development of health insurance in England and Germany. It put the doctors in a very false light. It excited public hostility against men whom the public were led to believe were acting from a selfish attitude rather than from a public spirited attitude; and, worst of all, the medical men lost their influence and leadership and had very little to say about the patterns of insurance that were established.

A second warning is addressed by your committee to pharmacists only and that concerns their relations with their medical *confrères* on the question of meeting the proposed legislation. Cooperate cordially with the medical men and dental groups only when these groups give definite promises of backing the modifications proposed by Pharmacy. The Majority Report (page 135) recommends

> The appropriate medical, dental, nursing and pharmaceutical societies should appoint committees to ascertain the facts regarding the provision of medical service, to study the various possibilities for extending the service and to prepare local and state plans accordingly.

Our association through its legislative committee or through our committee on socialized medicine should take immediate steps to secure a conference with similar committees of the State medical, dental and nursing societies, in order to frame a suitable program of coöperation in preventing drastic legislation on the subject of socialized medicine.

*3. Formulate Plans for a Conservative Type of Health Insurance.*—National Health Insurance has been in force in Great Britain since 1911 and while the plan met with violent opposition at the time of its inception, we learn from English friends whose opinions are much valued, that the project has given fairly satisfactory results. The following information as to the British Act was furnished by Mr. Thomas Lewis in 1931 and was published in the A. PH. A. JOURNAL of that year:

> "I have mentioned the National Health Insurance Act and would like to give some idea of this. It was instituted in Britain in 1911 and under it all persons in employment not earning more than a certain wage must be insured against sickness. Each week both the employer and employee pay a certain fixed sum into the Insurance Fund by means of affixing a stamp to a card supplied to each employee by the Government Department concerned; the employer deducts each week a sum (I believe about 18 cents) from the wage paid, adds to it his own payment and purchases an insurance stamp from the post-office for the total amount and fixes it to the card, canceling the stamp for further such use by dating it. The Government increases this amount by a further contribution of its own and this builds the National Health Insurance Fund. From this the employee obtains free medical treatment when sick and if unable to attend his work a certain weekly payment as well. Additional benefits added of late years are the supply of artificial teeth, spectacles and surgical appliances when prescribed by the physician. Suggestions have been made whereby the family of the insured person will also receive the same treatment at some future time by an adjustment of the Act.
>
> "The medical attention and the supply of medicines work in this way. The insured person is required to register with a physician who receives a payment of about two dollars per annum per insured person registered with him, whether he attends to the insured individual every day of the year or even if no medical attention is given at all. The physician, when necessary, writes a prescription which the sick person takes to any pharmacist on the Government Panel, and in this way receives what is prescribed, payment being made to the pharmacist by the Government through one or other of its Insurance Committees. It may be noted that no patent medicine or proprietary articles may be prescribed by the physician for insured persons. Payment is made to the pharmacist after the prescriptions have been priced by a pricing committee which proceeds to do the pricing for each drug separately according to an agreed National Price List, then adding to the total the dispensing fee which varies according to whether it is a mixture, ointment, gargle, etc., which has been prescribed. It is the duty of the Retail Pharmacists' Union to arrange these prices with the Government."

Mr. Hugh N. Linstead, secretary of the Pharmaceutical Society of Great Britain, has been good enough to furnish us the following additional information concerning the operations of Health Insurance in his country:

> 1. The British Medical Association informs me that 49.4 per cent of the medical practitioners of Great Britain are panel practitioners. They divide the medical practitioners into the following classes:
>
> | | |
> |---|---|
> | Consultants | 7.5 per cent |
> | Practicing as dentists | 1.1 per cent |
> | Insurance general practitioners | 49.4 per cent |
> | Non-insurance general practitioners | 22.9 per cent |
> | Whole-time officers of local government bodies, etc. | 14.6 per cent |
> | Unclassified | 4.5 per cent |
> | | 100.0 per cent |
>
> 2. As there are roughly 17,500,000 insured persons and 17,500 insurance practitioners the average number of insured persons for whom an insurance practitioner is responsible is 1000. At present the insurance practitioner is suffering from

a 10 per cent National economy cut in his payment and receives 8/1½d. per annum for each insured person for whom he is responsible instead of the basic capitation fee of 9/–. The average annual compensation is therefore £406. 5. 0.

3. About 99 per cent of the chemists' shops are on the Insurance Panels. The number in England and Wales is approximately 10,473. The number in Scotland is approximately 1300.

4. The average income for each shop is about £200 per annum, representing about 3/–. for each insured person.

Mr. Linstead also answered four questions as to the premiums paid by those workers who are beneficiaries of Health Insurance. He also kindly furnished us with a copy of the 32-page Bulletin of the Ministry of Health giving details of operation of the Health Insurance scheme. These data will be shown inquirers on request. In studying the above outline of British Health Insurance, it must be borne in mind that this insurance scheme applies to only 17,500,000 of the 44,000,000 inhabitants of Great Britain. According to first-hand information obtained by us, the Health Insurance payments to the retail pharmacist go a long way toward covering the overhead of the "chemist shop" and the purchases of the 26,500,000 uninsured furnish a reasonable income to the approximately 12,000 pharmacists of Great Britain.

## CONCLUSION.

The foregoing lengthy recital may be summarized as follows. Above we have discussed:

1. Data from the Report of the Committee on Cost of Medical Care.
   - (*a*) Majority recommendations of the Committee.
   - (*b*) Principal minority report.
2. Report of the Commission on Medical Education.
3. Relation of Pharmacy to these reports.
4. A program for Pharmacy.
   - (*a*) Pursue a "*laissez faire*" policy?
   - (*b*) Join physicians and dentists in fighting the proposed plans?
   - (*c*) Formulate plans for a conservative type of Health Insurance? This section of the report gives data concerning the operation of Health Insurance in Great Britain since 1911.

Organized pharmacy must be prepared not so much to fight the propositions outlined above as to see that adequate provisions of protection are given to our calling. The one encouragement that one obtains from a study of the situation is that the fate of the average practicing physician and of the practicing dentist is as much at stake as is that of the practicing pharmacist. The situation calls for organization in every county in the state of "professional guilds" such as Kings County has conducted with such distinct success during the past few years.

A secondary item is the proposition made last winter that a law be passed (*a*) limiting the sale of all medicines (patent and otherwise) to registered pharmacies; (*b*) prohibiting the sale of food, tobacco, etc., in registered pharmacies. Our direct information is:

1. That this type of legislation will not be hurriedly pushed through the legislature.
2. That one or two years of educational effort will be carried on prior to the introduction of the legislation.
3. That such legislation is bound to come up eventually.
4. That the project has been assured of ample financial backing.
5. That the group behind the movement is more than willing to coöperate with existing pharmaceutical organizations.

This matter is worthy of the careful attention of all of us having the interest of Pharmacy at heart.

# THE PROFESSIONAL PHARMACY.

## An Analysis of Prescription Department Activities.

BY FRANK A. DELGADO AND ARTHUR A. KIMBALL.

(This analysis of Prescription Department Activities is part of the National Drug Store Survey and published under and by authority of the U. S. Department of Commerce, Bureau of Foreign and Domestic Commerce. The table of contents will acquaint the readers with the valuable information on professional pharmacy contained in the report; information that has never before been given and offers studies of the various phases of the important subject for the pharmacists and students in colleges of pharmacy.

It is contemplated to print the report in four instalments. In due time notice will be given of the opportunity to secure reprints and it is suggested that readers make inquiry by addressing THIS JOURNAL as to how these reprints may be obtained, and the advantageous cost, if ordered in advance of completion of the report. Further information is given in the Foreword.—*Editor.*)

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## FOREWORD.

With the ever-increasing trend toward specialization in most fields of endeavor, it is not surprising to find in the retail drug field a specialist—the professional pharmacy. These establishments, in which the entire attention is centered on prescriptions, and other commodities and services devoted to the public health, are said to be growing in number, particularly in locations in which offices of physicians are concentrated. A concentrated group of physicians naturally is the source of a large volume of prescriptions, sufficient to keep several pharmacists busy. The many items of rare occurrence called for require a much more complete stock than is generally carried by the usual commercial type drug store. Often prescriptions which are very difficult to fill, and which require unusual skill and fairly frequent practice, are received. In the professional pharmacy such prescriptions can usually be delegated to a pharmacist who fills such prescriptions fairly frequently. A large prescription staff is also needed to supply the exacting service requirements of the physicians—prompt collecting of prescriptions and sufficient telephone equipment to receive prescriptions by telephone, prompt filling of prescriptions in spite of the large volume, prompt and special delivery service, keeping at hand information to answer physicians' questions in regard to new specialties and the like. Thus, there are many reasons justifying the strictly professional pharmacy. It is as important a part of any "medical" building or other concentration of physicians, as is the prescription compounding laboratory in a modern hospital.

Therefore, in order to obtain a complete picture of the prescription filling activities of pharmacy, this study of the professional pharmacy was included as an integral part of the National Drug Store Survey. The value of the information contained in this report is not believed to be confined to the proprietors of professional pharmacies. It contains much information which should be of practical value to the proprietors of commercial type drug stores, in increasing their volume of prescription business and the profit possibilities of their prescription departments. Professors and students in colleges of pharmacy may find herein answers to some of the questions

about which there has been conjecture. Drug wholesalers and manufacturers of pharmaceutical supplies should find the list of leading ingredients, which was compiled after an analysis of 20,000 prescriptions, of particular interest. Pharmacists who are contemplating the operation of a professional pharmacy will find certain information particularly directed to them. It is hoped, therefore, that all branches of the drug profession and trade will be in some way aided by the information presented in this report.

This report on the varied activities of the professional pharmacy is the second report from the National Drug Store Survey concerning the prescription department activities of the retail drug trade. The first report, published in 1932, was entitled "Prescription Department Sales Analysis in Selected Drug Stores," and concerned the professional activities of 13 commercial type drug stores in St. Louis, Mo.[1]

This present report on the activities of the professional pharmacy is to be printed in the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION in several instalments, starting in the July 1933 issue. It will then be made available through the office of the secretary of the AMERICAN PHARMACEUTICAL ASSOCIATION.

The proprietors of the various professional pharmacies analyzed herein kindly made available the records of their establishments, and the AMERICAN PHARMACEUTICAL ASSOCIATION (particularly E. F. Kelly, secretary of the ASSOCIATION, and E. G. Eberle, editor of the ASSOCIATION'S JOURNAL) made possible the publishing and distributing of the report. This study was made in the Merchandising Research Division of the Bureau of Foreign and Domestic Commerce, under the direction of H. C. Dunn, chief of that division, and Wroe Alderson, director of the National Drug Store Survey. Miss Ruby M. Sanders of the above division rendered valuable assistance in tabulating material contained herein.

## INTRODUCTION.

The purpose of this report is to present a complete picture of the professional pharmacy—the pharmacy which centers its attention almost entirely on prescriptions and other items related to public health. A study of the professional pharmacy is a necessary part of any complete analysis of the retail distribution of drug store commodities and services, such as has been undertaken in the National Drug Store Survey.

Of course, comparatively speaking, there are few professional pharmacies in the country. The actual number is a debatable question. However, Dr. C. B. Jordan, dean of the School of Pharmacy, Purdue University, who has made studies of professional pharmacies for a number of years and who is thus one of the best qualified to answer the question, places the number at slightly less than 400. One well-known trade journal has recently, at great effort, compiled a list of the 3200 largest prescription drug stores in the United States. But it is not stated that these 3200 stores are necessarily professional pharmacies. In any event, the number is not a large part of the approximately 60,000 retail drug stores in the United States.

As for a definition of the term "professional pharmacy," there would undoubtedly be differences of opinion. Would only stores in which the entire volume consisted of prescriptions and other items related to public health be included, or would stores which enjoyed both a large prescription business and a large business of a commercial type be included? Or, again, would stores with a small prescription business, but which had the definite purpose of building up only the professional phase be considered professional pharmacies? For the purpose of this report, only those pharmacies in which the majority of the business is in prescriptions, and in which only the professional phase is promoted will be considered professional pharmacies. If half of a store's volume is in prescriptions, it is probable that the store is filling a sufficiently large number of prescriptions daily to be classed as a professional pharmacy. The fact that a professional pharmacy has a soda fountain, or carries cigars and cigarettes, as a convenience to its patrons, should not rob the pharmacy of its professional character, as long as these lines are carried strictly as a matter of convenience. Particularly for professional pharmacies located in professional buildings, it is sometimes necessary to have a soda fountain and the like for the convenience of the physicians and others who frequent the building. However, none of the four St. Louis professional pharmacies which form the basis of this report had soda fountains.

[1] Available at office of Superintendent of Documents, Washington, D. C.

Four professional pharmacies located in St. Louis, Mo., were the test laboratories in which this detailed analysis was made. A large phase of this study was centered around a complete analysis, from every practical point of view, of 10,000 prescriptions filled by two of these four pharmacies. Also, wherever such information would be of interest and value, the findings in the professional stores are compared with those of the 13 commercial type drug stores analyzed in the first report on the professional phase of the National Drug Store Survey. Ten thousand prescriptions filled by the commercial type stores are analyzed and compared with the 10,000 prescriptions filled by the professional pharmacies. In addition to this material, a questionnaire containing 65 questions was sent to a large number of proprietors of professional pharmacies and was answered in full by 35 professional pharmacists. These questionnaire replies add a great deal to the supply of information concerning the professional pharmacy, and make it possible to present an even more complete picture than was at first contemplated.

To give an idea of how "professional" the pharmacies included in the survey are, it might be stated that in the four St. Louis pharmacies, over 73 per cent of the total volume was in actual prescription business, these stores averaging from 112 to 219.4 prescriptions each per day, exclusive of liquor prescriptions. The 35 "questionnaire stores" had an average of 63 per cent of the total business represented by prescriptions, and averaged 73 prescriptions each per day. These figures might be compared with those of the 13 commercial type stores analyzed in the first report on the prescription phase of the Survey, which averaged only 15.3 prescriptions each daily, exclusive of liquor.

Various estimates of the total number of prescriptions filled in the United States annually have been made, ranging from 120,00,000 to 300,000,000. A recent exhaustive private survey placed the number at close to 165,000,000, including refills. This would mean that the 60,000 retail drug stores in the United States fill an average of less than 8 prescriptions each per day. However, as there are many pharmacists who make no special effort to obtain prescription business, and in fact many drug stores filling an average of as few as one prescription a day, there are many times eight prescriptions a day available to those pharmacists who strive for prescription business. Taking the average prescription business of the professional pharmacy as that reported by the 35 questionnaire stores, 73 prescriptions per day, and using Dr. Jordan's estimate of the number of professional pharmacies in the country, slightly less than 400, it can be estimated that between 10,000,000 and 11,000,000 prescriptions are filled annually in professional pharmacies. This would mean that professional pharmacies, less than 1 per cent of the total number of retail drug stores, fill between 6 and 7 per cent of the 165,000,000 prescriptions filled annually in the United States.

From the solely business viewpoint, the operation of the professional pharmacy would appear to be a profitable venture. The four St. Louis professional pharmacies studied had annual sales volumes averaging over $107,000 each, on which they averaged over $10,000 net profit each. Of course, St. Louis is a large city, and is outstanding in the way its physicians and patients support professional pharmacies, but the study in these four stores at least shows the possibilities of profit in prescription business when a store is able to maintain a large enough volume to operate as a professional pharmacy.

The number of professional pharmacies in the United States is slowly increasing, and it is believed that in the future the trend will be toward an even larger number of these pharmacies, with an increasing proportion of the total prescription business handled by professional pharmacies. One reason for this conclusion is the inauguration of the four-year course in colleges of pharmacy, effective as of this year. It hardly seems reasonable that students will continue to enroll in colleges of pharmacy in the same number as heretofore with no higher object in view than the opening of the usual commercial type drug store. Also, in addition to the professional prestige to be gained, there are a number of monetary reasons which will cause many pharmacists to prefer to operate a professional pharmacy. For one thing, the competition is not as great, for the present at least. There is less chance of encroachment by other types of establishments, such as grocery stores and department stores. Also, the hours in the professional pharmacy are inclined to be shorter than in the commercial type drug store. The majority of the 35 "questionnaire" professional stores opened at 8:00 A.M. and closed at 10:00 P.M. on week days and had average Sunday hours of from 9:00 A.M. to 8:00 P.M., but some of those stores had even shorter hours.

Naturally, the number of professional pharmacies will always be limited. Small towns,

and towns and cities where there is considerable dispensing on the part of physicians, will not present a good location for the embryo professional pharmacist. The proprietors of the 35 "questionnaire" stores estimated, on the average, that 20,000 people was the minimum population necessary to support a professional pharmacy. However, half of these 35 proprietors believed that 10,000 or less was a sufficient population for this purpose. Of course, a concentration of physicians' offices, particularly in a "medical" building, will always offer a fine opportunity for the establishment of a professional pharmacy. In an eastern city, for example, there are three "medical" buildings located within a space of two blocks, and each of these three buildings supports a professional pharmacy. However, there are examples of very successful professional pharmacies located quite some distance from the district where physician's offices are centered. Such is the case, for example, in Baltimore, Washington, New York, Detroit and St. Louis. St. Louis possesses two professional pharmacies located far from the "medical" buildings, yet both stores have a big prescription business and stand high in the esteem of physicians.

A professional pharmacy cannot be developed merely by having beautiful fixtures, a complete stock and delivery and other equipment. The professional pharmacist, probably to a greater extent than his more commercially minded brother druggists, will have to go out and bring in business. The methods employed by the professional pharmacist, it is true, will be different. They will be dignified and professional, and in the main will consist in calling on physicians to win their friendship and inspire their confidence. Of course, the prospective operator of a professional pharmacy must first select a suitable location, and must obtain a well-rounded stock, the basis of which may be the list of leading ingredients included in this report.

Among the factors responsible for the success of professional pharmacies are the following:

1. Knowledge and judgment, skill, experience, honesty, diligence, courtesy and personality of both the proprietor and his staff.
2. Physicians' support, coöperation, confidence and friendship.
3. Location, accessibility to physicians.
4. Store arrangement, appearance and cleanliness; adequate equipment.
5. Careful buying; quality, variety, purity and freshness of stock.
6. Accuracy in filling prescriptions; reasonable prices commensurate with quality and service; factors of selling.
7. Dependable service, every possible facility, such as sufficient telephone equipment, rapid calling for and delivery of prescriptions, prompt filling of prescriptions, prompt attention to mail orders, keeping new foreign and domestic preparations in stock.
8. Proper advertising and promotion, such as continual contact with physicians, meeting with and speaking before physicians and internes, furnishing prescription blanks.
9. Administrative ability—bookkeeping, adequate records, annual inventories and profit and loss statements, careful extension of credit, prompt collection of bills.

Nearly all of the factors enumerated above embrace the two outstanding phases of merchandising, cost control and sales promotion, in addition to the professional requirements. Thus, the proprietor of the professional pharmacy must be a good merchant, a capable business man, as well as a trained professional man. It is certainly true that in most cases the proprietors of professional pharmacies are leaders in the profession of pharmacy in their respective cities, and in some cases are national leaders in their profession. Professional pharmacists seem to be fairly young at the time they open their stores. Seventy-one per cent of the 35 pharmacists answering the questionnaire were younger than 40 when they opened their stores; 38.7 per cent were under 30.

### DESCRIPTION OF SURVEY STORES.

The four professional pharmacies comprising the test laboratories around which the major portion of this report is centered are located in the uptown business district in St. Louis, Mo. This uptown district is a busy business center, containing the theatrical center and many small shops. The four pharmacies are located within a space of two blocks, which fact does not seem to limit their sales volume, for all four stores had large volumes of business, averaging over $107,000 each per year. Three of the four pharmacies are located in buildings which are almost entirely devoted to offices of physicians, dentists and members of allied professions. The surrounding nearby area has quite a few physicians' offices. Thus there is a justifiable reason for these professional stores to locate in this high-rent business district.

None of the four establishments handled candy, cigars, cigarettes and other products of a nonprofessional type, with the exception of a limited line of toilet goods and articles. The prescription business in these stores accounted for from 59 to 88 per cent of their total sales volume, the remaining volume being devoted to hospital supplies and other items related to public health.

Three of the four pharmacists were located on the ground floor, while the other was located on the second floor of a building devoted mainly to physicians' offices. As to the amount of space necessary for the operation of a professional pharmacy it might be stated that this would depend on the particular establishment. One of the St. Louis pharmacies has a floor space of about 985 square feet (41 by 24 feet) in the principal room. Of this space, about 240 square feet are used for prescription work, 175 square feet for customers' space and 120 square feet for office space. In adjacent rooms the pharmacy has about 700 square feet, of which about 150 square feet are used for manufacturing, 200 square feet for prescription files and the balance for lockers and storage. There is also a space of about 120 square feet in the basement for storage.

Another of the test stores has a room measuring 17 by 30 feet (150 square feet) on the first floor, devoted entirely to compounding, stock and a waiting room for customers. This store has 18 feet of counter space for compounding and a corresponding amount of shelf space running 6 feet above the counter. In the basement this store has a space 30 by 50 feet (1500 square feet) in size, of which 15 by 15 feet (225 square feet) is devoted to its laboratory and the balance used for storage.

Another test store has a space of 36 by 16 feet (576 square feet) in the main portion of the store. There is a 15-foot balcony in the rear, underneath of which is the store's precription department space, about 15 by 20 feet (300 square feet), with appropriate shelving in every available space. In the center of this space is a 5-foot prescription counter and bookkeeper's desk (standing). There is also a 12-foot counter at the front of this space. The basement dimensions are the same as the floor above. There is a space at one end of approximately 225 square feet fitted with a laboratory table where all the heavy compounding and manufacturing is done. In addition, there is a hallway space of about 8 by 20 feet connecting the basement with an outside elevator, the larger portion of which is utilized for the storage of prescription ware, etc.

The other test store has a space of about 860 square feet (36 by 33 feet) with a 12-foot prescription counter in the rear. There is a width of 5 feet between the prescription counter and the wall cases in the rear. The office is on a balcony 15 feet long and extending out 8 feet from the wall. There is a 3-foot extension of the balcony around two sides of the store. The basement comprises 806 square feet, of which 120 square feet is used for manufacturing activities, and the balance for prescription files and storage.

Thirty-five professional pharmacists answering a questionnaire gave among other replies a statement concerning the size of their stores. The 35 pharmacies occupied an average of 1632 square feet, although the typical size was 1075 square feet. The largest sized store occupied 10,320 square feet; the smallest, only 308 square feet.

### DESCRIPTION OF QUESTIONNAIRES ANSWERED BY 35 PROFESSIONAL PHARMACISTS.

Dr. C. B. Jordan, Dean of the School of Pharmacy of Purdue University, has conducted a study of professional pharmacies in each of the four years from 1929 through 1932. The material for these studies has been gathered by means of questionnaires sent to a fairly complete list of professional pharmacists throughout the country. For Dr. Jordan's 1932 study, one of the authors of this report was kindly permitted to prepare a questionnaire consisting of 66 questions with subdivisions making a total of 130 questions. Dr. Jordan sent this questionnaire to approximately 400 professional pharmacists, 40 of whom returned it. Only in the case of 35 of the 40 was the questionnaire answered nearly complete. These 35 questionnaire returns are used for the basis of the supplemental material for this report. The authors greatly appreciate Dr. Jordan's efforts and those of J. L. Weinland, extension worker, in the School of Pharmacy at Purdue University, who analyzed these voluminous questionnaires.

Various data from the questionnaire replies are inserted throughout the report wherever it is interesting and valuable to compare the findings in the four test stores with those in other professional pharmacies. A complete report on this questionnaire survey, containing the composite answers to each of the 66 questions, was published by Dr. Jordan in the November 1932 issue of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION. However, the answers

to most of the questions will be found in various sections of this present report, where references are made to the "questionnaire stores."

FIXTURE AND PRESCRIPTION INVENTORY REQUIREMENTS IN OPENING A NEW STORE.

The fixture investment was only ascertained for two of the four survey test stores. Store A in 1930 valued its equipment at $2912 and in 1931 at $1907, having written off $1005 because of depreciation. This fixture investment will undoubtedly seem very small for such a professional pharmacy, but it should be remembered that store A has been in business for many years and the fixture investment shown gives the depreciated value. Store B valued its fixtures at $6236 in 1930, and at $5873 in 1931, having written off $363 for depreciation. Store B is a fairly new store, and the fixture value shown is probably at a figure somewhat approaching the cost price when purchased.

The minimum fixture investment for 29 of the 35 "questionnaire" stores averaged $5964, which seems high. The typical value, however, was $3000. One professional pharmacist reported a fixture investment as low as $300, and one over $15,000. The range was as follows: 13 stores had fixtures valued at from $300 to $2500; 6 stores from $2591 to $5000; 7 stores, $5001 to $10,000; 2 stores from $10,001 to $15,000; and one over $15,000. The fixture investment for both professional and commercial type pharmacies varies greatly. Some conservative proprietors open with a modest investment in fixtures and make improvements as the business warrants them.

In an eastern city there are three professional pharmacies under one management. One of these stores has a fixture and equipment investment of $5510, made up of the following items: Wooden fixtures (wall cases, show cases, etc.), $3500; soda fountain and carbonator, $1600; biological refrigerator, $221; and miscellaneous, $75. The fixture cost in this store was high, due to the peculiar shape which made it necessary to make the wooden fixtures to order. The fixtures in the newest of the three stores, a beautiful modern store, amounted to only $3800, this store not having a soda fountain. The third store had a fixture investment of $5800.

A modest eight-foot mahogany veneer prescription display case used to divide the store front and rear was purchased by one of the "questionnaire" stores for $300 at the factory. This sum did not include cases and other fixtures. The proprietor of this quite presentable little professional pharmacy was of the opinion that one could open a professional pharmacy with a fixture investment of as low as $1000.

*Equipment Necessary for the Prescription Department.*—It would require about $150 to purchase the equipment necessary to stock a prescription department. About half of this sum is taken up by the scales. The laws in different states and cities set up certain minimum requirements for scales sensitivity. Therefore, this is a subject which is not entirely optional with the pharmacist. It would seem, however, that professional pride alone would prompt him to use a scale of unquestioned accuracy. Certain items in the list will seldom be used by the pharmacist, and by some will be deemed of insufficient importance to warrant their purchase. These items are indicated by a footnote. It will be noted that there is no reference in the following list of equipment to the cost of labels, a necessary prescription department expense. This is a matter which will have to be decided by the individual pharmacist. However, it has been observed that pharmacists generally are inclined to spend too much on this item. It is believed that it would be a good policy to purchase in the beginning a very small assortment of labels, allowing future business to dictate the extent of further purchases. No typewriter is included in the list, nor is other office equipment. Many pharmacists purchase a second-hand typewriter at the start, which they use until business warrants the purchase of a new one. The list of necessary equipment for the prescription department follows:

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| Prescription scales, sensitive to $^1/_{20}$ gr. or 3 mg. (medium price, but good) | $63.00 |
| Dispensing scales (for larger quantities) | 22.50 |
| A set of apothecaries' weights ($^1/_2$ gr. to 1 oz.) | 2.15 |
| A set of metric weights (10 mg. to 50 Gm.) | 2.31 |
| A set of at least 5 graduates (60 minim, 4 ounce, 8 ounce, 1 pint and 1 quart) | 3.29 |
| A set of at least 2 graduates (125 cc. and 250 cc.) | 1.25 |
| Wedgwood mortars and pestles [one No. 2 (16 oz.) at $1.32, and one No. 10 (10 pints) at $6.36] | 7.68 |
| Glass mortars and pestles, assorted (2 oz. size for $0.34, 4 oz. at $0.40, 8 oz. for $0.55 and | |

| | |
|---|---|
| 16 oz. for $0.50; 6 inch for $0.68 and 8 inch for $0.84) | 2.14 |
| Steel spatulas, assorted (3 inch for $0.38, 5 inch for $0.50, 6 inch for $0.68 and 8 inch for $0.84) | 2.40 |
| 1 rubber or composition spatula (6 inch for $0.50) | 0.50 |
| Bunsen burner (estimated cost) | 1.00 |
| A pill tile (porcelain, 10 by 12 inches) | 1.80 |
| A pill roller[1] | 0.38 |
| A pill finisher (estimated cost)[1] | 1.00 |
| A water-bath (estimated cost)[1] | 1.00 |
| A set of funnels (2 oz. for $0.14, 4 oz. for $0.16 and 8 oz. for $0.22) | 0.52 |
| A ring stand or funnel support (estimated cost) | 1.00 |
| A percolator (glass—1/2 gallon)[1] | 1.20 |
| Three stirring rods (6 inch for $0.02, 8 inch for $0.03, 10 inch for $0.04) | 0.09 |
| Filter paper (three packages of different sizes) | 2.20 |
| Three flasks (100 cc. to 500 cc.) | 0.64 |
| Two evaporating dishes (diameter, 4 inch for $0.38 and 8 inch for $0.67) | 1.05 |
| All standard sizes of empty capsules (1 box 100 in each of 8 sizes) | 1.59 |
| Three boxes of powder papers (two plain and one waxed) | 1.41 |
| All standard sizes (1/2 oz. to 16 oz.) of prescription bottles with good grade corks or other closures (390 bottles in 8 sizes) | 9.24 |
| All standard ointment jars (three of each of five sizes ranging from 1/2 oz. to 4 oz.) | 0.64 |
| One dozen ointment tubes, small sizes, assorted tips | 0.65 |
| One moderately fine sieve[1] | 0.75 |
| Two prescription files to hold 500 to 1000 prescriptions | 2.50 |
| A poison register | 1.25 |
| An exempt narcotic record (estimated cost) | 1.00 |
| Pill boxes (9 doz. assorted pasteboard; and green glass capsule vials (4 doz.)) | 3.02 |
| One gross assorted powder boxes (4 sizes) | 2.45 |
| Six dozen folding cartons (sizes 1 oz. to 16 oz.) | 0.67 |
| Nine dozen capsule slides (3 sizes assorted) | 0.70 |
| Total equipment investment | $144.97 |

[1] These items would by some be considered unnecessary.

No biological refrigerator has been included in the list of equipment, due to the diversity of opinion on this subject. Some stores opening with a small prescription business purchase a small refrigerator for as little as $10 or $25. Others reserve a section of their fountain refrigerator for the storage of biologicals.

The United States Pharmacopœia X specifies that diphtheria and tetanus antitoxins shall be preserved at a temperature between 4.5° and 20° C. (40° and 68° F.), preferably the lower limit, and that smallpox virus be kept at the lowest possible temperature, preferably below 0° C. (32° F.), and never above 5° C. (41° F.). The same storage conditions should apply to all other biologicals. Some states have regulations covering this phase of biological merchandising. If the dealer has failed to provide proper storage and officials have condemned all or part of his stock of biologicals, the manufacturer cannot be expected to reimburse him for the loss. One manufacturer's catalog offers two all steel biological refrigerators, cork insulated, with respective capacities of 75 pounds and 150 pounds of ice, for $43.50 and $67.70, respectively, f.o.b. the factory.

*The Pharmacist's Library.*—In some states, drug stores are required to possess the current editions of the United States Pharmacopœia and the National Formulary. However, it would seem that the pharmacist would have sufficient pride in his profession to maintain some semblance of a professional library, even if not required by law. Most of the survey stores had a fair assortment of reference books and when approached on the subject, expressed interest in a list of books which might form a standard pharmacist's library. It is believed that the accompanying list of reference books, a composite list drawn from all of the survey stores, should fill the library requirements of the average drug store, even if falling considerably short of some of the excellent libraries possessed by some of the nation's leading professional pharmacists. The pharmacist

should not labor under the delusion that his library is an extravagance. He should consider it a necessary investment, just as necessary as his scales or other prescription equipment. The library will pay dividends, in one way as a safeguard against the possibility of error.

The accompanying list is only supposed to cover the essentials. Those interested will experience no difficulty in adding to the list such books as "Practical Uranalysis and Urinary Diagnosis," Ruddiman's "Incompatibilities in Prescriptions," a book on pharmaceutical Latin, pharmaceutical arithmetic, a manual on toxicology and a local medical directory. It is not necessary to say that the pharmacist should have copies of regulations pertaining to narcotics and intoxicating liquors, and the sanitary code of his particular city. The total cost of the books listed below would be approximately $75, considering the purchase of only one out of each set of bracketed books, of which the pharmacist should choose one.

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| Pharmacopœia of the United States[1] | $4.00 |
| The National Formulary[2] | 3.50 |
| New and Non-Official Remedies[3] | 1.50 |
| Pharmaceutical Recipe Book[2] | 5.00 |
| Useful Drugs[3] | 0.60 |
| Merck's Index[4] | 2.50 |
| The United States Dispensatory[1] | 15.00 |
| [ Remington's Practice of Pharmacy[1] or | 10.00 |
| Arny's Practice of Pharmacy[5] or | 8.00 |
| Caspari's Practice of Pharmacy[6] | 7.50 |
| Pharmaceutical Syllabus[2] | 2.25 |
| U. S. P.-N. F. Prescription Ingredient Survey[2] | 2.00 |
| Basic Material for a Pharmaceutical Curriculum[7] | 4.00 |
| 4000 Years of Pharmacy[1] | 5.00 |
| The Art of Compounding[8] | 4.00 |
| [ Treatise on Commercial Pharmacy[1] or | 4.50 |
| Drug Store Business Methods[6] | 2.75 |
| The Cost of Medicines[9] | 2.50 |
| [ Pharmaco-Therapeutics, Materia Medica and Drug Action[10] or | 15.00 |
| Pharmacology and Therapeutics[5] | 7.50 |

[1] Agent and publisher is the J. B. Lippincott Co., Philadelphia, Pa.

[2] Published by the American Pharmaceutical Association, Baltimore, Md.

[3] Published by the American Medical Association, Chicago, Ill.

[4] Published by Merck and Co., Inc., Rahway, N. J.

[5] Published by W. B. Saunders Co., Philadelphia, Pa.

[6] Published by Lea and Febiger, Philadelphia, Pa.

[7] Published by McGraw-Hill Book Co., Inc., New York, N. Y.

[8] Published by P. Blakiston's Son & Co., Inc., Philadelphia, Pa.

[9] Published by the University of Chicago Press, Chicago, Ill. (A brief abstract of this report is available to interested persons upon request to the publishers.)

[10] Published by D. Appleton and Co., New York, N. Y.

*Necessary Financial Outlay in Opening a New Store.*—In the last chapter of this report a list of leading chemicals, galenicals, botanicals, etc., based on the study of 20,000 prescriptions, is presented. If only those ingredients which occurred five times or more each in 10,000 prescriptions were purchased on the opening order, the cost would be $605.77. This is believed to be a sufficient opening stock for the average commercial type drug store, and the basic stock for a professional pharmacy. In fact, it is believed that a conservative pharmacist would find the list of ingredients occurring at least ten times each a sufficient opening order for a commercial type pharmacy. These ingredients would have a total cost of only $387. This information is presented in detail in Chapter VII.

The cost of fixtures and prescription department equipment has been presented above, and it has been seen that a presentable and not under-equipped drug store can be opened for a comparatively small sum, in fact, a much smaller sum than is often spent by pharmacists, who are

often inclined to make a large opening investment without waiting to see the amount warranted by the store's progress.

As based on experience, the 35 "questionnaire" professional pharmacists reported that it would require an average investment of $7264 to open a professional pharmacy. The typical opinion was that an investment of $5000 would be sufficient.

### ASSOCIATION MEMBERSHIP.

Membership in professional and trade associations, both national and local, should be indulged in by the pharmacist. Furthermore, he should strive to attend their meetings, for the amount of benefit he derives will correspond to his own participation and contribution. The sum of $25 a year is not too large for this purpose and should be regarded as a necessary and justifiable expenditure. Seven of the commercial type test store proprietors spent an average of $54 a year for association dues, one proprietor spending as high as $160.

### WINDOW DISPLAYS AND OBSERVANCE OF "PHARMACY WEEK."

Three of the four professional pharmacies providing the principal test laboratories for this study are located on the ground floor and have show windows. The field force, however, failed to observe more than a minimum attempt to take full advantage of these windows by frequent changes of the display contained therein. The tendency was to place a few ornamental jars containing brightly colored chemicals in the windows and to leave them there.

It was not ascertained to what extent the four St. Louis professional pharmacies studied observed "Pharmacy Week." However, 31 of the 35 questionnaire stores answered a question to this effect, 23 of the 31 stating that they did observe "Pharmacy Week." However, it is believed that pharmacists as a whole are not observing "Pharmacy Week" or installing sufficiently professional and educational window displays, and they are urged to give these subjects further consideration. A national association which for the past several years has published and given to retailers lithographed maps and "back drops" portraying colleges of pharmacy, world distribution of chemicals, botanicals, etc., has found that only 8000 to 10,000 of the approximately 60,000 retail druggists in the country use the material. If all druggists would coöperate, the association would continue the work. But so many druggists have refused to use the material or to join in the observance of "Pharmacy Week" that the members of the association have become somewhat discouraged in their effort to aid the retail pharmacist.

### REQUIREMENTS OF THE PRESCRIPTION CONTAINER.

The question as to the advisability of using glass containers or pasteboard boxes for capsules, pills and tablets and various chemicals, is not one which lends itself to scientific analysis in this type of a survey. However, as this is a question of considerable interest to the profession, the opinions of several chemical and pharmaceutical manufacturers and others who have sought the answer to this question were obtained.

Proponents of the glass containers maintain that such containers are air-tight, and that pasteboard boxes are not; that capsules themselves are not air-tight and are subject to deterioration; and that a large number of chemicals are subject to chemical or physical change when coming into contact with moisture, which reaction can only be prevented by the use of air-tight glass containers. They further contend that inasmuch as the average druggist is not familiar with all the chemicals affected by moisture, the only safe course is to put up all chemicals, tablets, capsules, etc., in glass containers.

One impartial authority, who has made detailed scientific observations on this subject, says that these conclusions as to the superiority of air-tight glass containers over pasteboard boxes are correct, but adds that the cheapness of pasteboard boxes make their use desirable when stable chemicals such as quinine are dispensed. However, with deliquescent chemicals (which are set forth in the U. S. Pharmacopœia) such as potassium acetate, air-tight glass containers are indicated, according to this authority. He further says that chemicals affected by light and not by the action of air can well be dispensed in opaque pasteboard boxes.

One chemical manufacturer states that the general policy of his firm is to supply chemicals in the most economical package, consistent with the requirements for the protection of the particular chemical. Glassware being more expensive, items are only packaged in bottles when

necessary. This manufacturer made a test of more than 600 chemicals for light sensitivity, and submitted a list of 50 chemicals which according to these tests required light protection when supplied in glass containers. However, while the other items may be immune from the composition of light, when mixed together a chemical reaction might take place in the presence of light. Many other chemicals which are light sensitive were not included in the test inasmuch as they are furnished in cans and cartons. It is further suggested that possibly it would be better to package pills and capsules composed of light sensitive items in containers protected from light, which could be a box, a can or a bottle of colored glass, although the glass container has a better appearance and possibly is more convenient to use. This manufacturer formerly used amber glass, but is now using jet black containers, which have proved satisfactory.

The technicians of another manufacturer advise that a pasteboard box for capsules, pills and tablets appears to be more convenient for the consumer than a screw cap bottle; that unless the bottle has a wide mouth (is really a jar) it is often difficult to get a capsule out of the bottle, particularly if it sticks. They further state that the theoretical advantage of an air-tight glass bottle over a pasteboard box is greatly diminished in the usual practice, when the bottle is opened several times a day. This manufacturer also emphasizes the greater expense of the glass container.

Nine of the 35 questionnaire professional pharmacies used boxes for capsules, pills, etc., 8 used bottles for these items and the other 18 firms used both bottles and boxes. Seventeen firms favored corks, 16 favored screw caps and 2 used both types of closures for bottles. Only 5 of the 35 pharmacies had their name stamped on their bottles.

## CHAPTER I. SALES, EXPENSE AND PRESCRIPTION BUSINESS IN THE PROFESSIONAL PHARMACY.

### SALES, EARNINGS AND OPERATING FACTORS IN FOUR PROFESSIONAL PHARMACIES.

The sales volume, net profit and operating factors of four professional drug stores are presented in Table I. For Stores A and B, the results shown are for the year 1930 as well as for 1931, so that changes over a two-year period may be noted. It will be seen that the sales volume in Store A dropped appreciably in 1931 as compared with 1930, while Store B had an almost corresponding increase over the two-year period. Note the change in the operating expense and net profit ratios to sales in Stores A and B over the two years. These ratios seem to reflect careful management, for in spite of the large decrease in sales in one store and the increase in the other, the operating expense was trimmed or expanded so that it maintained an almost constant relationship to sales. The operating expense of these drug stores is broken down into more detail in Table II, where it is shown by types of expense.

It is interesting to note the uniformity between the stores as to the gross margin percentages. Only Store C was out of line, its gross margin amounting to only 37.8 per cent of sales, which thus left a much smaller reservoir out of which to pay operating expenses and take a net profit. Nevertheless, Store C made a good margin of net profit, due to its low cost of operation. In case the average gross margin for these professional pharmacies, amounting to 45.7 per cent of sales, seems a little low for exclusive prescription pharmacies, it should be remembered that this is the gross margin for the entire business of these stores, and not just the prescription business alone. In Store A, for example, the nonprescription business amounted to over 40 per cent of the total sales volume, as will be seen in Table IV. Although gross margin is an important factor in profit production, this table certainly shows that it is not the only important factor.

The case of Store D certainly shows clearly the importance of watching the store's operating expense to keep it trimmed down to a reasonable figure. Store D had the highest gross margin of any of these professional drug stores and yet it produced the smallest margin of net profit, only 2.8 per cent of sales. Its turnover was about average, so the high operating expense was not due to that factor. Reference to Table II will disclose the types of expense which were unusually high in Store D, running the operating expense up to the point where it consumed 46.4 cents on every dollar of sales. The pharmacist should always keep in mind the fact that every additional dollar of operating expense means that there will be a dollar less of net profit.

The turnover figures shown represent the financial turnover, that is, the number of times that the money invested in the average inventory was turned during the year 1931. Although it is

generally conceded that a high turnover gives better profit possibilities and is a sign of efficient operation, it will be seen that high turnover is not an absolute essential in these professional pharmacies. Store C had the lowest turnover rate and at the same time the lowest operating expense in proportion to sales. However, Store C would undoubtedly benefit by simplification of its inventory and should get rid of many "dead" items by methods suggested in a later section of this report, devoted to inventory simplification. The sales volume of Store C was about the same as that of Store B, and yet Store C's turnover was 1.8 times less per year.

An agency in St. Louis made a study of the operations of 40 commercial type drug stores during 1931. These stores were for the most part located in residential communities, although a few were situated at traffic intersections in business subcenters. These stores had an average annual sales volume of $32,180; their average gross profit amounted to 32.3 per cent of sales; average operating expense was 31.1 per cent of sales; average net profit, 1.2 per cent of sales; and their average stock turnover, 3.1 times a year. It is interesting to compare these operating results with those shown in the table for the four professional stores. The professional stores were certainly operated at greater net profit than these commercial type stores, having an average net profit of over $10,000 each, as compared with an average net profit of only $383 for the commercial type stores. The gross profit of the commercial type stores was considerably less than in the professional stores, but of course the commercial type stores did a much smaller proportion of prescription business with its higher percentage of gross profit.

The questionnaire stores (referred to in the introduction) had a decrease in sales volume in 1931 as compared with 1930, in 20 out of the 32 stores about which this question was answered. The other 12 showed an increase in volume in 1931.

TABLE I.—SALES, EARNINGS AND OPERATING FACTORS IN PROFESSIONAL DRUG STORES.

| Store. | Annual Sales Volume. | Turnover. | Per Cent of Total Sales Volume. Gross Margin. | Operating Expense. | Net Profit. |
|---|---|---|---|---|---|
| A (1930)..... | $136,928 | [1] | 46.2 | 34.6 | 11.6 |
| A (1931)..... | 123,321 | 3.6 | 46.5 | 36.2 | 10.3 |
| B (1930)..... | 92,863 | [1] | 47.7 | 37.0 | 10.7 |
| B (1931)..... | 107,425 | 4.4 | 47.9 | 34.1 | 13.8 |
| C (1931)..... | 106,678 | 2.6 | 37.8 | 27.8 | 10.0 |
| D (1931)..... | 78,142 | 3.2 | 49.2 | 46.4 | 2.8 |
| Average.... | $107,560 | 3.3 | 45.7 | 35.5 | 10.2 |

[1] The turnover for 1930 was not obtained.

OPERATING EXPENSE BREAKDOWN IN PROFESSIONAL DRUG STORES.

The breakdown of operating expense into the various types of expense making up the total is shown in Table II. Operating expense is shown in this table as a percentage of the sales volume of the particular store concerned, in order that comparison may be made between the stores. The operating expense summary is given for four professional pharmacies for the year 1931, and in order that a two-year period can be noted, the expense summary for 1930 is also given in the case of Stores A and B. This latter comparison shows some interesting facts, in view of the fact that the sales volume of Store A decreased about $13,600 in 1931 over 1930, while during the same period Store B showed an increase in sales amounting to about $14,500. It is interesting to note which expenses maintain a constant ratio to sales and which increase or decrease in the face of increased or decreased sales volume. It should be mentioned that this expense summary was obtained from the operating statements of the stores concerned, and in some cases the grouping of expenses in one store did not exactly correspond with another. For example, while Stores A and B showed "laundry" as a separate item, Stores C and D grouped this cost under "general expenses."

It will be seen that Store C had by far the lowest operating expense ratio to sales. This was partly due to the fact that its salary cost was low, particularly "officers' salaries," but even if this cost was raised to the average, the total expense ratio of Store C would remain the lowest. This low operating cost enabled Store C to make a good net profit in spite of a gross margin considerably below the other stores.

Of course, the outstanding expense items are salaries, rent and delivery expense. The last column in the table shows the per cent of the total expense accounted for by each type of expense. It will be seen that 60.3 per cent of the cost of operating the professional pharmacies was accounted for by salaries, 13.9 per cent by rent and 11.8 per cent by delivery expense.

In Store A for 1931, officers' salaries showed a large increase and employees' salaries a corresponding decrease over the previous year. This is due to the fact that certain members of the staff who in 1930 were classified as employees were made officers of the firm in 1931, so that their salaries were placed under "officers' salaries" in the latter year. This was done to secure a lower rate on employees' compensation insurance.

In case the delivery expense in Stores C and D seems surprisingly low as compared with Stores A and B, it should be remembered that Stores A and B placed drivers' and delivery boys' wages under "delivery," rather than under "salaries," thus raising the delivery expense item considerably.

The advertising expense of Store D is many times greater than in the other stores. More money was spent on advertising in Store D than was spent for rent. Less than one-third of this advertising expense was due to the cost of prescription blanks. The store advertised in the newspapers and circularized doctors as a part of its advertising campaign. The total operating expense in Store D was considerably higher than that of any of the other stores, this high expense being caused principally because of the high salary and advertising costs. In view of the fact that the net profit in Store D amounted to only 2.8 per cent of sales, it would ordinarily seem that the advertising expense amounting to 6.4 per cent of sales was a sign of inefficient management. However, it might prove to be a reasonable expenditure if the proprietor of the store purposely sacrificed present earnings in order to build up a large volume in the future. If Store D had this purpose, the expenditure may be justified. Store D had the smallest volume of the four professional stores in spite of the fact that it has been in business for eight years, this being the fourth year in its present location. But such a large advertising expense would not be justified just for the present business it brings in.

Note that the delivery expense in Store A was not pared down in 1931, so in view of decreased sales volume its percentage of sales was considerably higher in 1931. In Store B the amount spent for delivery in 1930 seemed to be sufficient to provide delivery service for the increased sales of 1931, so the delivery expense percentage was lower in 1931.

It is interesting to compare the operating expense of these professional pharmacies with that of the 40 commercial type drug stores referred to earlier. The operating expense of these 40 stores averaged 31.1 per cent of sales. Owner's salary amounted to 7.7 per cent of sales; wages averaged 11.2 per cent of sales; rent averaged 5.1 per cent of sales; advertising 1.1 per cent of sales, and miscellaneous expense (including taxes, insurance, repairs, depreciation, and heat, light and power, etc.) averaged 6 per cent of sales. Delivery expense was not shown for the 40 commercial type drug stores, but in 10 other similar stores it was found to be a negligible expense, amounting to only one-tenth of 1 per cent of sales.

Thus, almost the entire difference in expense between the professional and commercial type pharmacies is accounted for by the heavy delivery expense of the professional pharmacies. Owner's salary, wages and advertising expense were slightly higher in the professional stores, and rent was slightly lower, while miscellaneous expense was considerably lower in the professional stores, when considered as a percentage of sales volume.

While the per cent of rent to sales was only slightly lower in the professional pharmacies, it should be kept in mind that these commercial type stores were located in residential communities and subcenters, thus having a lower percentage of rent. The professional stores, on the other hand, were located in the heart of the theater district uptown, where rents are considerably higher. Thus, it is more practical to compare the professional store rents with rents of commercial type stores located in the same section of the city, which had an average rent amounting to 6.6 per cent of sales volume.

Inasmuch as the professional pharmacy does not generally have to depend on transient trade, it would seem unnecessary for them to occupy premises in a location which has high-priced rentals. The four pharmacies studied in this report located in this expensive district due to the fact that many physicians have offices in this district, and not because of the transient trade which comes to a business center. As is shown later in this report, much of the business of the profes-

sional pharmacy is received by telephone, the prescriptions being delivered to the patient, so that these customers actually visit the store only on rare occasions. Professional pharmacies can locate on upper floors, not requiring the more expensive ground floor space, and at locations somewhat removed from the heart of the business district, and save a considerable amount on rent, and yet not lose much of their potential business. The professional pharmacy generally locates in a building devoted to doctors' offices, or at least nearby, but generally physicians do not cluster in a high-rental business district, as did these physicians in St. Louis.[1]

The questionnaire stores (the 35 professional pharmacies referred to in the introduction) paid rent averaging 6.5 per cent of sales, the range being from 3 to 11 per cent of sales. It is interesting to note that the store paying the highest rent, $1000 a month, was second lowest when rent is considered as a per cent of sales, its rent amounting to only 3.5 per cent of sales. Of the 35 stores, 24 have stores on the ground floor and 11 have stores upstairs. Sixteen of the 35 questionnaire stores are located in medical arts buildings.

TABLE II.—BREAKDOWN OF OPERATING EXPENSE IN PROFESSIONAL DRUG STORES.

| | Per Cent of Total Sales Volume. | | | | | | | Per Cent of Total Expense, All Stores. |
|---|---|---|---|---|---|---|---|---|
| Type of Expense. | Store A (1930). | Store A (1931). | Store B (1930). | Store B (1931). | Store C (1931). | Store D (1931.) | Average. | |
| Salaries | 21.07 | 21.81 | 20.29 | 19.11 | 17.42 | 31.06 | 21.38 | 60.3 |
| Officers | 3.45 | 12.32 | 10.88 | 9.54 | 5.62 | 14.62 | 8.94 | 25.2 |
| Employees[1] | 17.62 | 9.49 | 9.41 | 9.57 | 11.80 | 16.44 | 12.44 | 35.1 |
| Rent | 3.29 | 3.65 | 7.75 | 6.70 | 4.91 | 4.10 | 4.93 | 13.9 |
| Power, Heat, Light, etc | 0.33 | 0.36 | 0.48 | 0.38 | 0.53 | 0.59 | 0.43 | 1.2 |
| Delivery | 5.62 | 6.20 | 5.16 | 4.55 | 0.82 | 1.40 | 4.18 | 11.8 |
| Advertising | 0.96 | 0.96 | 0.47 | 0.50 | 0.63 | 6.40 | 1.42 | 4.0 |
| General[2] | 0.45 | 0.48 | .. | .. | 0.58 | 4.43 | 0.82 | 2.3 |
| Prescription Blanks[3] | 0.51 | 0.48 | 0.47 | 0.50 | 0.05 | 1.97 | 0.60 | 1.7 |
| Telephone and Telegraph | 0.40 | 0.42 | 0.44 | 0.36 | 0.49 | 0.40 | 0.42 | 1.2 |
| Insurance | 0.61 | 0.49 | 0.34 | 0.33 | 0.80 | 0.31 | 0.50 | 1.4 |
| Interest | .. | .. | .. | .. | 0.10 | .. | 0.02 | 0.0[5] |
| Depreciation | 0.72 | 0.82 | 0.38 | 0.34 | 0.73 | 0.37 | 0.59 | 1.7 |
| Laundry | 0.15 | 0.20 | 0.25 | 0.29 | .. | .. | 0.16 | 0.4 |
| Taxes and Licenses | 0.30 | 0.32 | 0.25 | 0.19 | 0.22 | 0.32 | 0.27 | 0.8 |
| Postage | 0.10 | 0.10 | 0.08 | 0.13 | 0.78 | .. | 0.20 | 0.6 |
| Amortization of Leasehold | .. | .. | 0.54 | 0.47 | .. | .. | 0.15 | 0.4 |
| General Expenses[4] | 1.06 | 0.89 | 0.56 | 0.75 | 0.38 | 1.40 | 0.83 | 2.3 |
| Total Operating Expense | 34.61 | 36.22 | 36.99 | 34.10 | 27.81 | 46.35 | 35.48 | 100.0 |

[1] In Stores A and B this item does not include drivers' and delivery boys' wages, which are placed under "Delivery."

[2] Includes donations.

[3] Stores C and D designated this item as "stationery and printing."

[4] Includes such items as repairs, freight and express, and in Stores C and D laundry.

[5] Less than $^5/_{100}$ of 1%.

PRESCRIPTION BUSINESS RECEIVED BY TELEPHONE.

Store A has three telephones at an average expense of $14 each per month. About 15 per cent of this store's prescription business is received over the telephone from physicians. About 30 per cent of the total prescription business consists of refills telephoned in by customers and delivered to them. This store does not have private lines to the offices of physicians, and the

[1] Information of this type can be obtained by consulting the Store Location Studies conducted in connection with the National Drug Store Survey.

proprietor does not believe this expense would be justified. About the same situation is reported for Store B, which had three telephones including one coin telephone.

Store C has six telephones, two of which are coin telephones, and the total telephone bill amounts to about $36 a month. From 15 to 20 per cent of the total prescription business comes by telephone, according to the proprietor's estimate. This store has private lines to the offices of two physicians, but the proprietor does not believe that the expense is justified.

Store D has two telephones which cost about $14 each and one pay station which does not cause the store any expense. The prescription business received by telephone in this store is very important as it amounts to about 50 per cent of the total prescription business. This store has no private lines to physicians' offices. As to whether or not private telephones of this sort are justified, the proprietor makes reference to a pharmacy in Louisville which gave this scheme a year's trial and then abandoned it.

Four of the questionnaire stores had direct telephone lines to physicians' offices, and in three of these cases it was reported that the cost was warranted. Thirty, or 88.2 per cent of the 34 stores concerning which this question was answered, did not maintain such private telephone lines. As an average for 32 questionnaire stores, 26.6 per cent of their prescription business was received by telephone, and 29.9 per cent of the prescriptions filled were delivered.

### TIME STUDY OF PRESCRIPTION BUSINESS IN THREE PROFESSIONAL PHARMACIES.

The following table is presented to give a picture of the flow of the prescription business in three professional pharmacies, according to various periods of the day from the time they opened until they closed in the evening. In Stores A and C the period from 3:00 to 6:00 P.M. had the largest number of prescriptions, but the two preceding periods, from 11:00 A.M. to 1:00 P.M. and from 1:00 to 3:00 P.M. really had the heaviest volume inasmuch as each of these periods is only two hours in length as compared with the three hours between 3:00 and 6:00 P.M. In Store D the two periods running from 11:00 A.M. to 3:00 P.M. were clearly outstanding.

In Stores A and C, the opening period from 8:00 to 11:00 A.M. and the closing period from 6:00 to 9:00 or 10:00 P.M., both being at least three-hour periods, clearly had the lighest volume of prescription business. In Store D, the closing period, from 6:00 to 10:00 P.M. had the lightest volume, but the opening period in the morning had quite heavy volume. Thus it can be said that the professional pharmacy, generally speaking, will have its heaviest volume of prescription business from 11:00 A.M. to 3:00 P.M., and its lightest volume in the evening after 6 o'clock and during its opening period in the morning. Of course, in individual cases, such factors as store location may vary the time of day in which business is heaviest, but as professional pharmacies generally have a central location, most of them will probably encounter the same conditions as are shown in the table.

It will be seen that the delivery service is an important factor in the professional pharmacy. From 26 per cent (in Store C) to 43.6 per cent (in Store D) of the prescriptions were delivered. This, of course, represents an element of expense which must be taken into account when considering the profit possibilities of the professional pharmacy.

In Stores C and D, the Sunday hours were only half as long as the other days of the week, but the prescription business amounted to less than one-third of the usual daily volume. Store A was open from 9:00 A.M. to 4:00 P.M. However, practically the entire Sunday prescription work in this store is done within a three-hour period from 10:00 A.M to 1:00 P.M. It will be seen that it is not so essential for the professional pharmacy to keep the long hours kept by the commercial type drug store, and that it is not the prescriptions which are responsible for the long business day of the commercial type pharmacy. Students of pharmacy who feel a repugnance to the long 14-, 16- and 18-hour days of the commercial type pharmacy will be drawn to the professional pharmacy, where the hours are generally shorter, and in many cases could be made even shorter, by closing after 6:00 P.M. and on Sundays when the volume of prescription business is so light that there is no necessity of remaining open. In many cases it would probably be more profitable to close the establishment than to keep it open in the evening and on Sunday, in view of the light volume of prescription business. It is not unreasonable to suppose that shorter hours in the drug business would attract a desirable type of young men.

The week considered for Store A was in April 1932, while a week in April 1933 was the time when this study took place in Stores C and D. The proprietor of Store D stated that business

in that store was at a low ebb during the week of this study and that the volume would normally be 20 per cent greater. The entire month of April 1932 was studied in Store A, but for the first week refills were not considered. When refills were considered the entire volume showed a considerable increase. The first period of the day, from 8:00 to 11:00 A.M., seemed to be the most affected by the inclusion of refills in the study, leading to the conclusion that the greater portion of this early morning business was occasioned by fairly regular customers bringing in prescriptions to be refilled while on their way to work.

As for the questionnaire stores, while there was a wide variation in the time at which these stores open and close, the majority opened at 8:00 A.M. and closed at 10:00 P.M. on week days, while the average Sunday hours are from 9:00 A.M. to 9:00 P.M. Two of the stores do not open on Sunday. As for the Sunday prescription business, 1 store reported that it is heavy, 3 that it is good, 5 that it is only fair and 24 that it is poor.

TABLE III.—PRESCRIPTION BUSINESS IN THREE PROFESSIONAL PHARMACIES ACCORDING TO THE TIME OF DAY IN WHICH THEY WERE FILLED.

| Day. | Number of Prescriptions Including Refills and Percentages by Time of Day. | | | | | | | | | | | | Number of Deliveries. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 8 to 11 A.M. | | 11 A.M. to 1 P.M. | | 1 to 3 P.M. | | 3 to 6 P.M. | | 6 to 9 P.M.[1] | | Total Day. | | |
| | Number. | Per Cent. | Number. | Per Cent. | Number. | Per Cent. | Number. | Per Cent. | Number. | Per Cent. | Number. | Per Cent. | |
| *Store A.* | | | | | | | | | | | | | |
| Monday | 28 | 13.9 | 46 | 22.9 | 47 | 23.4 | 62 | 30.8 | 18 | 9.0 | 201 | 100.0 | 51 |
| Tuesday | 41 | 20.0 | 43 | 21.0 | 46 | 22.4 | 57 | 27.8 | 18 | 8.8 | 205 | 100.0 | 62 |
| Wednesday | 31 | 19.1 | 36 | 22.2 | 37 | 22.8 | 40 | 24.8 | 18 | 11.1 | 162 | 100.0 | 62 |
| Thursday | 20 | 11.0 | 39 | 21.6 | 41 | 22.7 | 61 | 33.7 | 20 | 11.0 | 181 | 100.0 | 53 |
| Friday | 36 | 19.4 | 36 | 19.4 | 35 | 18.8 | 60 | 32.3 | 19 | 10.1 | 186 | 100.0 | 50 |
| Saturday | 19 | 8.8 | 47 | 21.9 | 78 | 36.3 | 46 | 21.4 | 25 | 11.6 | 215 | 100.0 | 60 |
| Sunday[2] | 50 | 100.0 | .. | .. | .. | .. | .. | .. | .. | .. | 50 | 100.0 | 16 |
| Average daily[3] | 29 | 15.1 | 41 | 21.4 | 48 | 25.0 | 54 | 28.1 | 20 | 10.4 | 192 | 100.0 | 56 |
| *Store C.* | | | | | | | | | | | | | |
| Monday | 41 | 19.6 | 39 | 18.7 | 47 | 22.5 | 51 | 24.4 | 31 | 14.8 | 209 | 100.0 | 62 |
| Tuesday | 24 | 14.5 | 41 | 24.7 | 33 | 19.9 | 45 | 27.1 | 23 | 13.8 | 166 | 100.0 | 45 |
| Wednesday | 32 | 17.6 | 38 | 20.9 | 37 | 20.3 | 43 | 23.6 | 32 | 17.6 | 182 | 100.0 | 43 |
| Thursday | 29 | 16.3 | 42 | 23.6 | 39 | 21.9 | 38 | 21.3 | 30 | 16.9 | 178 | 100.0 | 47 |
| Friday | 30 | 15.1 | 40 | 20.1 | 45 | 22.6 | 49 | 24.6 | 35 | 17.6 | 199 | 100.0 | 43 |
| Saturday | 33 | 15.0 | 37 | 16.8 | 51 | 23.1 | 56 | 25.5 | 43 | 19.6 | 220 | 100.0 | 59 |
| Sunday[4] | 53 | 100.0 | .. | .. | .. | .. | .. | .. | .. | .. | 53 | 100.0 | 23 |
| Average daily[3] | 32 | 16.7 | 39 | 20.3 | 42 | 21.9 | 47 | 24.5 | 32 | 16.6 | 192 | 100.0 | 50 |
| *Store D.* | | | | | | | | | | | | | |
| Monday | 26 | 20.5 | 25 | 19.7 | 25 | 19.7 | 25 | 19.7 | 26 | 20.4 | 127 | 100.0 | 65 |
| Tuesday | 22 | 19.0 | 37 | 31.9 | 28 | 24.1 | 20 | 17.2 | 9 | 7.8 | 116 | 100.0 | 43 |
| Wednesday | 24 | 21.6 | 27 | 24.3 | 30 | 27.0 | 20 | 18.0 | 10 | 9.1 | 111 | 100.0 | 46 |
| Thursday | 25 | 24.0 | 34 | 32.7 | 35[5] | 33.7[5] | [5] | [5] | 10 | 9.6 | 104 | 100.0 | 43 |
| Friday | 32 | 32.7 | 21 | 21.4 | 20 | 20.4 | 15 | 15.3 | 10 | 10.2 | 98 | 100.0 | 44 |
| Saturday | 29 | 27.4 | 28 | 26.4 | 33 | 31.1 | 10 | 9.4 | 6 | 5.7 | 106 | 100.0 | 47 |
| Sunday[4] | 33 | 100.0 | .. | .. | .. | .. | .. | .. | .. | .. | 33 | 100.0 | .. |
| Average daily[3] | 26 | 23.6 | 29 | 25.5 | 28 | 26.4 | 15 | 13.6 | 12 | 10.9 | 110 | 100.0 | 48 |

[1] This period is from 6:00 to 10:00 P.M. in Stores C and D.

[2] Total day, open from 9:00 A.M. to 4:00 P.M. only.

[3] Sunday not included.

[4] Total day, open from 9:00 A.M. to 4:00 P.M. only.

[5] Prescriptions filled from 1:00 to 3:00 P.M. and from 3:00 to 6:00 P.M. are grouped together.

SHARE OF THE PRESCRIPTION DEPARTMENT IN SALES VOLUME.

As an average for the four professional stores, purely prescription business represented 73.13 per cent of total sales volume, as will be seen in Table IV. In the 13 commercial type drug stores,

as reported in the first prescription department report, the prescription sales volume averaged only 16.39 per cent of total store sales volume.

Stores A and B did not keep a record of their refill prescriptions at the time when the prescriptions studied were filled. However, they have since recognized the importance of such records for efficient operation of the department and kept a daily record of refills for several months. On the basis of these records there are estimated to be about 50 per cent as many refills as new nonnarcotic prescriptions in Stores A and B. In the case of Store D, refills were estimated to represent one-third of the total number of prescriptions filled and narcotics were estimated to amount to 7½ per cent of all prescriptions filled. However, in Store C the figures given for all types of prescriptions are based on an actual count of the prescriptions.

To determine the dollar sales volume for each type of prescription the number of prescriptions filled was multiplied by the average price of prescriptions of that type. The average prices of the different types of prescriptions in each store were determined by the study of a large number of sample prescriptions. Thus, while the percentages of sales volume accounted for by the different types of prescriptions as shown in Table IV are estimated figures, the method used in estimating them is believed to be of sufficient accuracy that there is no important variation from the actual figure, which it was impractical to obtain.

While the sales volume from liquor prescriptions amounts to a considerable proportion of the total sales of these stores, it should be remembered that the high average price per liquor prescription enables a relatively small number of prescriptions to bring in a large volume of sales. For example, in Store D regular prescriptions brought in 52.17 per cent and liquor prescriptions 27.27 per cent of the total sales volume. Yet Store D filled only 7103 liquor prescriptions as compared with 40,886 regular prescriptions.

Store A had the largest proportion of sales volume coming in from other than prescriptions. The proprietor of this store estimates that about one-third of this nonprescription business is in packaged medicines and goods and the other two-thirds in hospital supplies. None of these four stores had a soda fountain or carried tobacco or candy, and only a skeleton line of toiletries. Therefore, the 26.87 per cent of the business not accounted for by prescriptions mostly represents hospital and surgical goods, physicians' supplies, infant and invalid foods, biologicals, proprietaries and other items related to public health.

In the questionnaire stores (referred to in the introduction) on the average, 63 per cent of the total business was in prescriptions and the other 37 per cent nonprescription business. The typical proportion of the business accounted for by prescriptions, however, was 70 per cent. Only 25 of the 35 questionnaire stores answered this question. Nineteen of these stores sold patent medicines, while 16 did not. Seventeen operated soda fountains and sold candy, tobacco and toilet preparations, while 18 did not carry these nonprescription lines.

TABLE IV.—SHARE OF PRESCRIPTION DEPARTMENT AND CERTAIN TYPES OF PRESCRIPTIONS IN TOTAL SALES VOLUME OF PROFESSIONAL STORES.

| | | Per Cent of Total Store Sales Volume. | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | Regular Prescriptions Consisted of— | | |
| | | All | Liquor | Regular | | Nonnarcotics. | |
| Store. | Total Store Annual Volume. | Prescriptions. | Prescriptions. | Prescriptions. | Narcotics. | New. | Refills. |
| A..... | $135,398[1] | 59.06 | 9.70 | 49.36 | 4.54 | 29.88 | 14.94 |
| B..... | 99,415[1] | 71.76 | 17.22 | 54.54 | 4.20 | 33.56 | 16.78 |
| C..... | 106,678 | 87.66 | 19.50 | 68.16 | 7.75 | 40.70 | 19.71 |
| D..... | 78,142 | 79.44 | 27.27 | 52.17 | 3.77 | 30.96 | 17.44 |
| Ave. | $104,908 | 73.13 | 17.24 | 55.89 | 5.13 | 33.71 | 17.05 |

[1] The 12-month period considered for Stores A and B was from May 1, 1930 to May 1, 1931. (In the other two stores the calendar year 1931 was the period studied.)

NUMBER OF PRESCRIPTIONS FILLED DAILY AND ANNUALLY, BY TYPE OF PRESCRIPTION.

The four professional pharmacies filled from 112 to 219.4 prescriptions, exclusive of liquor, each day. Comparatively few liquor prescriptions were filled by these stores, ranging from only 12 to 19.5 each per day. As Store A had eight registered graduates, each employed full time, and

no part-time employees, it will be seen that each would have to fill an average of 28 prescriptions per day, exclusive of liquor prescriptions. Store B had six full time employees, and they would also average 28 prescriptions each per day. However, in each of these stores, one clerk handles all manufacturing of galenicals and other preparations, which consumes about half of his time, so that much clerical time would not be available for filling prescriptions. The proprietors of Stores A and B state that all of their clerks are necessary and are kept busy.

The questionnaire professional stores filled an average of 73 prescriptions each per day. Only 5 of the 33 proprietors answering this question stated that their stores filled more than 100 prescriptions daily, these 5 stores filling from 100 to 250 prescriptions each a day. These stores employ an average of 2.8 registered pharmacists and 5.5 nonregistered employees, an average of 8.3 employees per store. Nineteen stores have not reduced personnel during the depression, while 13 stores have reduced personnel.

The 13 commercial type drug stores studied and reported on in the first publication on the prescription phase of this study, filled an average of 15.3 regular prescriptions daily (1.7 narcotics, 9.7 new nonnarcotics and 3.9 refills) and 2.3 liquor prescriptions per day each. It is interesting to compare this showing for commercial type drug stores with the large daily volume of prescription business in the four professional pharmacies.

TABLE V.—NUMBER OF PRESCRIPTIONS FILLED, BY TYPES, DURING A YEAR, AND DAILY AVERAGE OF EACH.

| Type of Prescription. | Number of Prescriptions Filled. | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Store A. | | Store B. | | Store C. | | Store D. | |
| | Yearly Total. | Daily Average. | Yearly Total. | Daily Average. | Yearly Total. | Daily Average. | Yearly Total. | Daily Average. |
| Narcotics..... | 7,576 | 20.8 | 4,448 | 12.2 | 8,348 | 22.9 | 3,066[2] | 8.4[2] |
| New Nonnarcotics. | 48,334 | 132.4 | 37,660 | 103.2 | 47,779 | 130.9 | 24,191 | 66.3 |
| Refills..... | 24,167[1] | 66.2[1] | 18,830[1] | 51.6[1] | 23,623 | 64.7 | 13,629[2] | 37.3[2] |
| Total Regular Prescriptions.. | 80,077 | 219.4 | 60,938 | 167.0 | 79,750 | 218.5 | 40,886 | 112.0 |
| Liquor..... | 4,378 | 12.0 | 5,705 | 15.6 | 6,933 | 19.0 | 7,103 | 19.5 |
| Total, All Prescriptions, Including Liquor | 84,455 | 231.4 | 66,643 | 182.6 | 86,683 | 237.5 | 47,989 | 131.5 |

[1] Estimate, based on actual records kept since the field work on this survey.

[2] Proprietor's estimate.

NOTE: The year concerned for Stores A and B was from May 1, 1930 to May 1, 1931; for Stores C and D, the calendar year 1931 was studied.

PRESCRIPTION BUSINESS BY TYPE OF PRESCRIPTION IN 1910, 1920 AND 1930.

Table VI shows the breakdown of prescriptions, both narcotic and nonnarcotic, into official, mixed and specialty types in professional Stores A and B. A sample lot of prescriptions in each store serves as the basis of this analysis. In order to note any changes in the use of these different types of prescriptions over the past two decades, 1000 prescriptions filled by Store A in 1910, and another 1000 prescriptions filled by this store in 1920, were included in the study. The sample for 1930 consisted of 5170 prescriptions filled by Store A and 3500 filled by Store B.

It will be seen that there is little difference in the proportion of the total prescription business accounted for by each of the three types of prescriptions—official, mixed and specialty—between the two stores or within Store A in the three different periods. Despite the frequently asserted statement that specialty prescriptions have been supplanting official prescriptions, it will be seen that official prescriptions decreased only 2.2 percentage points from 1910 to 1930, while specialties also showed a decrease of 1.3 percentage points in the same period and mixed prescriptions show an increase of 3.5 percentage points. Approximately 25 per cent or slightly less than one out of four of the prescriptions included in this study for the twenty-year period called exclusively for specialties. This finding will come as a surprise to many members of the profession.

The decrease, although slight, was constant for both types of prescriptions, mixed prescriptions gaining the ground lost by the other two types. However, in Store B in 1930, official and

specialty prescriptions each represented a higher proportion of the total prescription business than they did in Store A for their high year, 1910. Therefore, it can be said that regardless of the store or the year, in the two stores studied official prescriptions represented a little more than half of the total prescription business when both narcotic and nonnarcotic prescriptions are considered, mixed and specialty prescriptions dividing the other half of the total about equally.

Of course, as might be expected, there were few narcotic specialty prescriptions, so official and mixed prescriptions had a resultant higher proportion of the total when narcotics alone are considered. It is not possible to show narcotics and nonnarcotics separately for 1910, as the Federal narcotic law was not in effect at that time and narcotics were not distinguished between or filed separately.

TABLE VI.—PRESCRIPTION BUSINESS BY TYPES OF PRESCRIPTIONS.[1]

| Prescriptions Studied. | Types of Prescriptions. All Prescriptions. Number. | All Prescriptions. Per Cent of Total. | Official. Number. | Official. Per Cent of Total. | Mixed. Number. | Mixed. Per Cent of Total. | Specialties. Number. | Specialties. Per Cent of Total. |
|---|---|---|---|---|---|---|---|---|
| Store A (1910)..... | 1000 | 100.0 | 531 | 53.1 | 233 | 23.3 | 236 | 23.6 |
| Store A (1920): | | | | | | | | |
| Narcotic..... | 150 | 100.0 | 76 | 50.7 | 60 | 40.0 | 14 | 9 3 |
| Nonnarcotic..... | 850 | 100.0 | 444 | 52.2 | 189 | 22.3 | 217 | 25.5 |
| Total..... | 1000 | 100.0 | 520 | 52.0 | 249 | 24.9 | 231 | 23.1 |
| Store A (1930): | | | | | | | | |
| Narcotic..... | 1078 | 100.0 | 778 | 72.2 | 259 | 24.0 | 41 | 3.8 |
| Nonnarcotic..... | 4092 | 100.0 | 1856 | 45.4 | 1127 | 27.5 | 1109 | 27.1 |
| Total..... | 5170 | 100.0 | 2634 | 50.9 | 1386 | 26.8 | 1150 | 22.3 |
| Store B (1930): | | | | | | | | |
| Narcotic..... | 500 | 100.0 | 347 | 69.4 | 119 | 23.8 | 34 | 6.8 |
| Nonnarcotic..... | 3000 | 100.0 | 1527 | 50.9 | 627 | 20.9 | 846 | 28.2 |
| Total..... | 3500 | 100.0 | 1874 | 53.6 | 746 | 21.3 | 880 | 25.1 |

[1] Private formula prescriptions not considered in this table.

PRESCRIPTION BUSINESS BY FORM OF PRESCRIPTION.

It is interesting to see the proportion of the prescription business represented by different forms of prescriptions. Table VII shows that over half of the prescriptions studied for 1930 were liquids. However, liquids were not quite as important in 1930 when they represented 52.65 per cent of the prescriptions studied, as they were in 1920 and 1910 when they accounted for about 64 per cent of the prescriptions studied. This loss by liquids was taken up by a gain in use for capsules and tablets over the 20-year period. Tablets showed a steady increase, representing only 5.9 per cent of the prescriptions filled in 1910, but 9 per cent in 1920 and 13.5 per cent in 1930. Capsules did not show a gain in use from 1910 to 1920, but showed a considerable increase in 1930. The percentage for liquids showed a much greater drop for nonnarcotics than narcotics, although the latter was considerable.

Although not as important, it might be noted that bulk powder showed a steady increase, its percentage of the total being twice as great in 1930 as in 1910. Other than liquids, the two forms showing the greatest decrease in use were divided powders and pills. Most of the decrease for divided powders occurred between 1910 and 1920.

For comparison with this showing for prescriptions filled in professional drug stores it is noted that in the case of 23,963 prescriptions filled by 13 commercial type drug stores in 1930, published in the first report on the prescription phase of the National Drug Store Survey, liquids represented 61.3 per cent of the prescriptions studied, capsules 17.5 per cent, tablets 9.9 per cent and ointment only 3.8 per cent. It will be seen that tablets and ointment had a less important part in the commercial type drug stores than in the professional stores, while the reverse was true for liquids.

Colleges of pharmacy might make good use of the findings shown in this table in allocating work to students. The increased use of tablet prescriptions can probably be accounted for by

specialty prescriptions. The increased popularity of glandular products would partially, but not entirely, account for the increase in the use of capsules. A number of manufacturers are featuring products packed in capsules and encouraging physicians to write for these under names that will designate them as the product of an individual manufacturer, and this is undoubtedly responsible in large part for the increased use of capsules. (See later sections of this report entitled "Specialty Capsule Prescriptions" and "Introduction of New Manufacturers' Specialties" which give information concerning the form of recent remedies placed on the market.)

TABLE VII.—PRESCRIPTION BUSINESS BY FORM OF PRESCRIPTION IN 1930, 1920 AND 1910.

| | Stores A and B (1930).[1] | | | | | |
|---|---|---|---|---|---|---|
| | Narcotic. | | Nonnarcotic. | | All Prescriptions. | |
| Form of Prescriptions. | Number of Prescriptions. | Per Cent of Total. | Number of Prescriptions. | Per Cent of Total. | Number of Prescriptions. | Per Cent of Total. |
| Liquid | 949 | 60.14 | 3616 | 50.99 | 4565 | 52.65 |
| Capsules | 337 | 21.36 | 1258 | 17.74 | 1595 | 18.40 |
| Tablets | 223 | 14.13 | 951 | 13.41 | 1174 | 13.54 |
| Ointment | 27 | 1.71 | 704 | 9.93 | 731 | 8.43 |
| Bulk Powder | .. | ... | 198 | 2.79 | 198 | 2.28 |
| Divided Powders | 13 | 0.82 | 126 | 1.78 | 139 | 1.60 |
| Pills | 4 | 0.25 | 95 | 1.34 | 99 | 1.14 |
| Effervescent Salts | .. | ... | 55 | 0.77 | 55 | 0.64 |
| Suppositories | 19 | 1.21 | 25 | 0.35 | 44 | 0.51 |
| Ampuls | 1 | 0.06 | 17 | 0.24 | 18 | 0.21 |
| Lozenges | .. | ... | 20 | 0.28 | 20 | 0.23 |
| All Other | 5 | 0.32 | 27 | 0.38 | 32[2] | 0.37 |
| Total | 1578 | 100.00 | 7092 | 100.00 | 8670 | 100.00 |

| | Store A (1920). | | | | | | Store A (1910). | |
|---|---|---|---|---|---|---|---|---|
| | Narcotic. | | Nonnarcotic. | | All Prescriptions. | | All Prescriptions. | |
| Form of Prescriptions. | Number of Prescriptions. | Per Cent of Total. | Number of Prescriptions. | Per Cent of Total. | Number of Prescriptions. | Per Cent of Total. | Number of Prescriptions. | Per Cent of Total. |
| Liquid | 103 | 68.67 | 545 | 64.12 | 648 | 64.80 | 637 | 63.70 |
| Capsules | 19 | 12.67 | 99 | 11.65 | 118 | 11.80 | 120 | 12.00 |
| Tablets | 20 | 13.33 | 70 | 8.23 | 90 | 9.00 | 59 | 5.90 |
| Ointment | 2 | 1.33 | 75 | 8.82 | 77 | 7.70 | 85 | 8.50 |
| Bulk Powder | ... | ... | 16 | 1.88 | 16 | 1.60 | 11 | 1.10 |
| Divided Powders | 3 | 2.00 | 16 | 1.88 | 19 | 1.90 | 42 | 4.20 |
| Pills | ... | ... | 20 | 2.35 | 20 | 2.00 | 26 | 2.60 |
| Effervescent Salts | ... | ... | 4 | 0.47 | 4 | 0.40 | 7 | 0.70 |
| Suppositories | 3 | 2.00 | ... | ... | 3 | 0.30 | 6 | 0.60 |
| Ampuls | ... | ... | 2 | 0.24 | 2 | 0.20 | .. | ... |
| All Other | ... | ... | 3 | 0.36 | 3[3] | 0.30 | 7[4] | 0.70 |
| Total | 150 | 100.00 | 850 | 100.00 | 1000 | 100.00 | 1000 | 100.00 |

[1] Does not include the 304 private formula prescriptions.

[2] Includes the following prescription forms: Narcotics, *units* five times; nonnarcotics, *granules* 11 times, *pearls* 7 times, *seed* 4 times, *pessaries* twice and *soap*, *cubes* and *plaster* each one time.

[3] Includes: *Granules* twice and *tampons* once, all nonnarcotic.

[4] Includes: *Plasters* twice, *paste* twice and *granules*, *tampons* and *konseal* each once.

## CHAPTER II. SEASONAL DEMAND FOR PRESCRIPTIONS.

Most manufacturers find that the slow or dull season for pharmaceuticals is during the summer months, due to the fact that there is less sickness in this season, this business generally increasing with the advent of fall. Table VIII shows this seasonal trend clearly, the volume in

both stores taking a considerable drop in the summer months, while the heaviest business was in the winter. While the usual commercial type drug store maintains its volume in the summer due to increased volume at the fountain and some other departments, the professional pharmacy does not have this diversification in types of products carried, so its total volume reflects the decreased volume in prescriptions and other lines connected with public health.

Health conditions of the country during the period covered by this survey were the best known for some time. As the pharmaceutical industry is governed more by public health conditions than by general business influences, the loss in volume during the current depression which has been less than that suffered by most industries, is more directly traceable to the good health conditions than to any other cause. The reputed general betterment of the public health must be taken into account when considering the future of prescription shops.

However, the proprietor of the professional pharmacy can profitably use any idle time which might accrue in the summer months, particularly August. Certain galenicals and other preparations can be manufactured for winter use. The spare time of the proprietor, or some other qualified person, can be utilized by "detailing" physicians and acquainting them with the store's services and products. This is also a good time to take inventory and to grant vacations to the members of the staff.

TABLE VIII.—TOTAL VOLUME OF SALES IN TWO PROFESSIONAL PHARMACIES, BY MONTHS.

| Month. | Total Sales Volume. Store A. | Store B. |
|---|---|---|
| 1930. | | |
| May | $11,552 | $7772 |
| June | 11,374 | 7612 |
| July | 10,610 | 7561 |
| August | 9,729 | 6780 |
| September | 10,661 | 7048 |
| October | 11,222 | 8156 |
| November | 11,036 | 8112 |
| December | 11,856 | 8205 |
| 1931. | | |
| January | 12,832 | 9477 |
| February | 11,432 | 9816 |
| March | 11,909 | 9307 |
| April | 11,185 | 9569 |
| Total | $135,398 | $99,415 |

SEASONAL DEMAND FOR REGULAR PRESCRIPTIONS.

The month by month volume of regular prescriptions (those other than liquor) is shown for four professional stores in Table IX. The calendar year 1931 is reported for Stores C and D and a twelve-month period starting May 1, 1930, is reported for Stores A and B. The fact that part of the months concerned are in 1930 for Stores A and B, and 1931 for the other two stores, makes no material difference. Thus, the total figure groups the prescription business by months, regardless of the year concerned.

The regular prescriptions tabulated in this table include both narcotics and nonnarcotics, and for Stores C and D, refills also. In all four professional stores, the months January through April had the heaviest volume, although May was also a heavy month in the case of Store A, and September through December also carried a heavy volume in Store C. The summer and late spring months were the lightest in all of these stores.

The last column of the table shows the proportion of the total number of regular prescriptions filled by the four professional stores falling into each month of the year. It will be seen that July, August and September were the three lightest months. These are the same months in which the total store sales volumes of Stores A and B were lightest, as shown in Table VIII.

For eight commercial type drug stores, reported on in the first publication on the prescription phase of the National Drug Store Survey, the three outstanding months as to number of regular prescriptions filled were February, January and March, respectively. Over 11 per cent of the

total number of regular prescriptions filled by these eight commercial type drug stores during the year studied were filled in February, 10.98 per cent in January, and 9.65 per cent in March. It is interesting to compare these commercial type store results with those for the four professional stores.

TABLE IX.—SEASONAL VOLUME OF REGULAR PRESCRIPTION BUSINESS IN FOUR PROFESSIONAL PHARMACIES.[1]

| Date. | Number of Prescriptions (Not Including Refills). Store A. | Store B. | Date. | Number of Prescriptions (Refills Included). Store C. | Store D. | Month. | Per Cent of Total in 4 Stores by Months, Regardless of the Year. |
|---|---|---|---|---|---|---|---|
| (1930) | | | (1931) | | | | |
| May | 5066 | 3235 | | | | | |
| June | 4788 | 2966 | January | 6846 | 3960 | January | 9.56 |
| July | 4412 | 2908 | February | 6195 | 3838 | February | 8.75 |
| August | 3950 | 2676 | March | 7817 | 3894 | March | 9.59 |
| September | 4309 | 2855 | April | 7132 | 3706 | April | 8.91 |
| October | 4551 | 3314 | May | 6484 | 3548 | May | 8.38 |
| November | 4343 | 3203 | June | 6339 | 3392 | June | 8.00 |
| December | 4772 | 3552 | July | 5491 | 3237 | July | 7.34 |
| (1931) | | | August | 5327 | 2770 | August | 6.73 |
| January | 5323 | 4777 | September | 6578 | 3006 | September | 7.66 |
| February | 4792 | 4306 | October | 7675 | 3254 | October | 8.60 |
| March | 4975 | 4291 | November | 6700 | 3091 | November | 7.93 |
| April | 4629 | 4025 | December | 7166 | 3190 | December | 8.55 |
| Total | 55,910 | 42,108 | Total | 79,750 | 40,886 | Total | 100.00 |

[1] Includes both narcotic and nonnarcotic new prescriptions in all four stores, plus refills in Stores C and D.

SEASONAL DEMAND FOR NARCOTIC AND LIQUOR PRESCRIPTIONS.

The volume of narcotic prescriptions in three professional stores is shown by months in Table X. The greatest demand for narcotic prescriptions in these stores was in January and February, followed by the months of March, April and December. There was much less demand for narcotic prescriptions in the summer and late spring months than in the winter.

Taking Store A individually, it was found that January produced an outstanding volume of narcotic prescriptions, more than twice as many as in July and August. January was also the outstanding month for this type of prescription in the case of Store B, nearly three times as many narcotic prescriptions being filled in January as in some of the summer months. But in the case of Store C, although January had a large volume of narcotic prescriptions, the leading months were December and February, followed closely by April and November.

In the prescription department report dealing with commercial type stores, narcotic prescriptions were tabulated by months for eight stores. In these commercial type drug stores, the largest volume of narcotic prescriptions was in the months December through April, over 14 per cent of the narcotic prescriptions filled during the year being filled in February, and 13.5 per cent in January.

The greatest demand for liquor prescriptions in four professional pharmacies taken together was in December, 13.44 per cent of the total number of liquor prescriptions filled in a year being filled in this month. December was clearly the outstanding month for this type of prescription for Stores A, C and D. However, Store B reversed this showing, filling the smallest number of liquor prescriptions in December.

For eight commercial type drug stores, the first prescription department report showed that 13.47 per cent of the liquor prescriptions were filled in December, almost exactly the same proportion as for the professional stores. For the commercial type stores, May and November were the next most outstanding months in this regard, although the sales volume in those months was not as outstanding as in October and November for the professional pharmacies, which months had the largest volume in the professional stores, December excepted.

TABLE X.—SEASONAL VOLUME OF NARCOTIC AND LIQUOR PRESCRIPTION BUSINESS IN PROFESSIONAL PHARMACIES.

| Month. | Narcotic Prescriptions of 3 Stores. Number of Prescriptions. | Per Cent of Total. | Liquor Prescriptions of 4 Stores. Number of Prescriptions. | Per Cent of Total. |
|---|---|---|---|---|
| January | 2282 | 11.20 | 1718 | 7.12 |
| February | 2139 | 10.50 | 1652 | 6.86 |
| March | 1935 | 9.50 | 2022 | 8.39 |
| April | 2002 | 9.83 | 1882 | 7.80 |
| May | 1520 | 7.46 | 1901 | 7.88 |
| June | 1397 | 6.86 | 1689 | 7.00 |
| July | 1316 | 6.46 | 1747 | 7.24 |
| August | 1198 | 5.88 | 1729 | 7.17 |
| September | 1314 | 6.45 | 1869 | 7.75 |
| October | 1672 | 8.21 | 2344 | 9.72 |
| November | 1724 | 8.46 | 2323 | 9.63 |
| December | 1873 | 9.19 | 3242 | 13.44 |
| Total | 20,372 | 100.00 | 24,119 | 100.00 |

*(To be continued next month)*

## TENTATIVE PROGRAM, CONFERENCE OF PHARMACEUTICAL ASSOCIATION SECRETARIES.

**Officers:** *President*, J. Lester Hayman, 325 Ash St., Morgantown, W. Va.; *First Vice-President*, Gustav Bachman, Minneapolis, Minn.; *Second Vice-President*, R. C. Wilson, Athens, Ga.; *Secretary-Treasurer*, Carl G. A. Harring, 20 Glen Road, Newton Center, Mass.; *Delegate to the House of Delegates*, Charles J. Clayton, Denver, Col. *Executive Committee:* Robert A. Lehman, Brooklyn, N. Y.; P. J. Garvin, New Haven, Conn.; J. W. Slocum, Indianola, Ia.; James J. Gill, Providence, R. I.

All sessions will be held in Hotel Loraine. First Session, Wednesday, August 30, 2:00 P.M., Colonial Room. Second Session, Friday, September 1, 2:00 P.M., Pompeian Room.

The Conference of Pharmaceutical Association Secretaries will try the plan of having no papers read but, instead, devote the sessions to round table discussions of timely topics. A list of topics follows, which may be added to.

1. Should the president be the directing head of the Association or should the Executive Committee be the governing body?

2. What form of program is most acceptable at conventions?

3. The resolutions that are submitted at annual meetings—who writes them? Should the secretary take an active part in preparing same?

4. Is it desirable to divide states into zones for the purpose of giving each zone representation in the presidency by rotation?

5. Should the functions of a secretary include that of contacting allied trades for the purpose of federation?

6. Is it possible to devise some plan whereby neighboring states may avoid holding conventions at the same time?

7. Contests and novel schemes for increasing interest in annual meetings.

8*a*. In what states are local and district meetings habitually held and what is the character of the programs at such meetings?

*b*. Are you following some concerted plan to link up these meetings with your State association for the purpose of increasing your membership?

9. What part do the drug trade salesmen play in the operation of State Pharmaceutical Associations and how can they function most satisfactorily—as associate members, or as independent affiliated organizations?

10. In what states are full-time secretaries employed? What are they paid? How are the necessary finances obtained? What do such full-time secretaries do to justify the compensation received? What states have abandoned full-secretary plan, and why?

11. What constructive thoughts have you received from these conferences, and what have you done to develop some of them for the benefit of your State association?

# EDITORIAL NOTES

Editor: E. G. Eberle, 10 West Chase Street, Baltimore, Md.

**Members of the Council, A. PH. A.:** S. L. HILTON, *Chairman;* CHARLES H. LAWALL, *Vice-Chairman;* E. F. KELLY, *Secretary;* H. V. ARNY, A. G. DUMEZ, H. A. B. DUNNING, WILLIAM B. DAY, C. E. CASPARI, J. H. BEAL, T. J. BRADLEY, AMBROSE HUNSBERGER. *Ex-Officio Members:* W. BRUCE PHILIP, *President;* ROWLAND JONES, G. H. GROMMET, *Vice-Presidents;* C. W. HOLTON, *Treasurer;* E. G. EBERLE, *Editor of the Journal;* A. G. DUMEZ, *Editor of the Year Book;* J. W. SLOCUM, *Chairman of the House of Delegates.*

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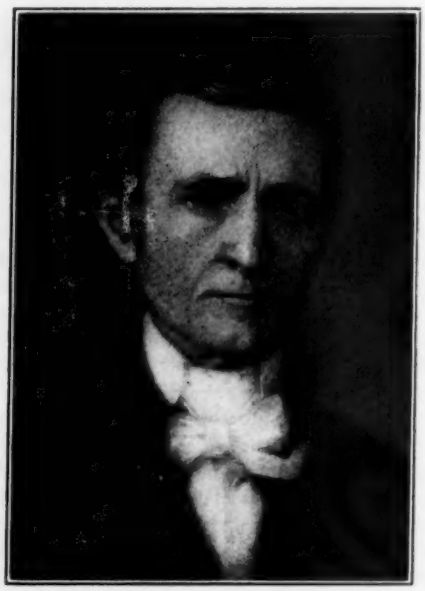
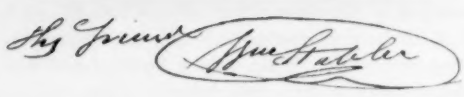
*On account of lengthy reports other matter had to be omitted from this issue of the* JOURNAL.

## THE LEADBEATER PHARMACY TO BE SOLD.

The Leadbeater Pharmacy in Alexandria, Va., was sold at auction, July 19th. It





dates back to the time of Washington, who was a patron here. **Richard H. Stabler,** a former owner, died November 18, 1878, aged 58 years. He was born and educated at Alexandria, Va., learned the drug business with his father, and afterward studied medicine at the University of Pennsylvania. He engaged in the drug business in Alexandria, and was elected professor of Pharmacy in the School of Pharmacy of the National Medical College, and afterward of the National College of Pharmacy at Washington. He became a member of the AMERICAN PHARMACEUTICAL ASSOCIATION in 1856, and was elected *President* for the year 1870–1871.

The apparatus, records, letters, shelf bottles, etc., were purchased for the AMERICAN PHARMACEUTICAL ASSOCIATION.

## THE BRITISH PHARMACY AND POISONS ACT.

A list of substances to be treated as poisons under the Poisons Act is to be prepared. An advisory committee to be known as the Poisons Board is to be formed for revising the schedule of prisons. Of the five persons to be appointed by the Pharmaceutical Society the following have been named: Secretary H. N. Linstead of the Society; Secretary Mallison of the Pharmaceutical Union and E. T. Neathercoat; the other two will be from the manufacturing interests and "company pharmacy."

## A LIFE OF SERVICE.

Dr. Frederick H. Baetjer, Baltimore, who died July 17th, gave his life in the service of science and humanity. He began his studies in the early days of X-ray experimentation, before the danger of its burns was fully understood, and continued his work after the result-

ing affliction necessitated his undergoing many surgical operations.

## PERSONAL AND NEWS ITEMS.

**O. A. Farwell** of Detroit was honored with the degree of Doctor of Science by the Detroit City College, June 9th.

**Bernard A. Bialk,** secretary, Detroit Branch, A. PH. A., was awarded the Honorary Degree of Bachelor of Science in Pharmacy from the Detroit Technical Institute.

**Dr. George H. Meeker,** dean of the Graduate School of Medicine, University of Pennsylvania, since he established it in 1918, was honored at a dinner, June 1st. A portrait of Dr. Meeker was presented to the university by Dr. George Morris Piersol on behalf of those in charge of medical affairs.

**Dr. A. Richard Bliss, Jr.,** has presented his resignation, effective August 15, 1933, as Chief of the Division of Pharmacology in the University of Tennessee to accept the position of Director of the Research Laboratories of the William A. Webster Company of Memphis.

**Dean A. G. DuMez,** of the School of Pharmacy of the University of Maryland, admits that it is possible to surprise him. The occasion was a surprise party tendered Dr. and Mrs. DuMez on their twenty-first wedding anniversary, June 9, 1933, by the Staff of the School of Pharmacy. A small chest of silver coin was presented to Dr. and Mrs. DuMez with the request that they purchase a tray to complete their silver service.

Those who attended the Toronto meeting of the A. PH. A. will remember meeting **Dr. V. E. Henderson,** professor of pharmacy and pharmacology at the University of Toronto. He has been elected an honorary member of the Kaiserliche Leopold Carolinische Deutsche Akademie der Naturforcher, the oldest scientific society in Germany, founded in 1652. Another honor that has come to Professor Henderson recently has been his reëlection as secretary of the American Society for Pharmacology and Experimental Therapeutics.

**K. K. Chen, G H. A. Clowes** and **Charles L. Rose,** Indianapolis, have determined that Amyl Nitrate is a better antidote than Methylene Blue for Cyanide poisoning.

Former President of the AMERICAN PHARMACEUTICAL ASSOCIATION, **C. Herbert Packard,** has been seriously ill for a month or more, but is now recovering, following an attack of influenza and pneumonia.

**Samuel C. Henry** was elected *president* and Julius Riemenschneider *vice-president* of the Chicago Veteran Druggists' Association on Jamieson Day. **Wilhelm Bodemann** delighted the members by his presence; he has, lately, been in poor health.

We are advised that Deans **W. F. Rudd** and **W. B. Day** are recovering rapidly after several weeks of hospital experience.

Anton von Hermann, aged 50 years, son of our fellow member **E. von Hermann,** died June 12th; the latter is *corresponding secretary* of the Chicago Veteran Druggists' Association. Sympathy is expressed.

**Dean R. A. Lyman** was taken suddenly ill June 11th, and removed to Bryan Hospital; we learn that he is rapidly recovering.

**Leon Monell,** *chairman* of the Committee on Pharmaceutical Economics, presented a comprehensive report before New York Pharmaceutical Association based on questionnaires of the year on the pharmaceutical activities in more than 500 drug stores. The report has been reprinted.

### MRS. CATHERINE DIEHL.

Mrs. Catherine Diehl died at her home in Louisville after a lingering illness, aged 85 years. Mrs. Diehl was the widow of Prof. C. Lewis Diehl, president of the AMERICAN PHARMACEUTICAL ASSOCIATION, 1874–1875, and the first Reporter on the Progress of Pharmacy elected by the ASSOCIATION in 1873. Mrs. Diehl is survived by three daughters: Mrs. Emily Frank, Miss Eleanor Diehl and Miss Jennie Diehl, several grandchildren and two brothers.

Professor Diehl died March 25, 1917, aged 77 years; this brings to mind the tributes expressed at the time of his death, for which see JOURNAL A. PH. A., for April 1917, and other numbers of the same year. See also a sketch in volume for 1916, page 119. For thirty-eight years he was Reporter on the Progress of Pharmacy, for twenty-eight years identified with the work on the National Formulary and for twenty-seven years with revisions of the U. S. Pharmacopœia.

American pharmacists will always remember him, and these few words, prompted by the passing of his helpmeet, are to remind us of her husband's great service to pharmacy. When the revisions of the U. S. Pharmacopœia and National Formulary are completed, the teachers of pharmacy may be prompted to speak of him to their students.

## SOCIETIES AND COLLEGES.

Local Secretary Emerson D. Stanley has supplied us with Madison photographs, some of which have been used in this number. Prof. Ralph W. Clark, of the University of Wisconsin, will supply you with highway maps for the asking.

Secretary Christensen reports that registration at the World's Fair is good—the highest record for one day is 170 pharmacists and 43 physicians.

By applying to the Visitor's Tourist Service Suite 1314–1321, Transportation Building, 608 So. Dearborn St., Chicago, you can have information relative to rates, routes, meeting place for friends, parking, etc.

See your R. R. Agent for special rates to Chicago and Madison.—Do not delay making inquiry.

### MADISON HOTELS.

Write the hotels or Secretary Emerson D. Stanley, 602 First Central Building, for reservations in Madison. The hotels are: Loraine, Park, Belmont, Madison, Capital, Fess, Cardinal; the Loraine is the headquarters hotel.

### SECTIONS OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.

See June JOURNAL for partial program of the Scientific Section and of the Section on Historical Pharmacy. For officers of the Sections see page X of the Roster in this issue of the JOURNAL.—*Write the officers and submit the titles of your papers.*

### TENTATIVE PROGRAMS.

#### SECTION ON EDUCATION AND LEGISLATION. PRELIMINARY LIST OF TITLES FOR MADISON MEETING.

**Officers:** *Chairman*, W. H. Rivard, Providence, R. I.; *Vice-Chairman*, P. H. Costello, Cooperstown, N. Dakota; *Secretary*, C. W. Ballard, Mt. Vernon, N. Y.; *Delegate to House of Delegates*, R. H. Raabe, Ada, Ohio.

"The Development and Preparaton of the New Pharmaceutical Syllabus," J. G. Beard.

"What Constitutes Good Teaching?" A. B. Lemon.

"An Opportunity and a Challenge to Pharmacy Educators," H. J. Goeckel.

"Pharmacy and Hospitals," Fred B. Kilmer.

"Public Health and Hospital Pharmacies," M. Dauer.

"The Pharmacy Board as the Sole Regulatory Body for Pharmacy," R. P. Fischelis.

#### SECTION ON PRACTICAL PHARMACY AND DISPENSING.

**Officers:** *Chairman*, W. Paul Briggs, 2121 H St., N.W., Washington, D. C.; *Vice-Chairman*, M. J. Andrews, Baltimore, Md.; *Secretary*, R. E. Terry, School of Pharmacy, University of Illinois, 701 S. Wood St., Chicago, Ill.; *Delegate to the House of Delegates*, I. A. Becker, Chicago, Ill.

"Variations in Hand-Moulded Hypodermic Tablets," by S. W. Bower.

"The Accuracy of Medicine Droppers with Flared Tips" and "The Protection of Prescription Labels with Lacquer," by Wm. J. Husa and Lydia M. Husa.

"A Preliminary Study of Capsule Tolerances," by Wm. F. Reindollar.

"Aromatic Elixir," by L. D. Havenhill and M. G. Smolt.

"The Prescription, the Physician and the Public," by L. W. Rising.

"The Relationships of Prescription Incompatibilities to Pharmacy," by Leon W. Richards.

"A New Method for Debittering Cascara Sagrada Extracts," by August J. Pacini.

"Useful Dental Prescriptions," by A. O. Mickelsen.

"Determination of the Reasonable or Permissible Margin of Error in Dispensing. II. Ointments," by Marvin J. Andrews.

"Hydrogen-Ion Concentration of Certain Galenical Preparations," by C. Jelleff Carr and John C. Krantz, Jr.

Dr. George D. Beal and Chester R. Szalowski have submitted a list for four titles to be credited to this Section but to be presented at the Joint Session. These are as follows:

"Notes on the Water of Crystallization of Quinine Sulphate."

"An Iodometric Assay for Organic Nitrites."

"A New Identity Test for Phenolbarbital."

"A Test for Gelatin in Agar."

#### SECTION ON HISTORICAL PHARMACY.

**Officers:** *Chairman*, Louis Gershenfeld, Philadelphia, Pa.; *Secretary*, C. O. Lee, Purdue University, Lafayette, Ind.; *Delegate to the*

*House of Delegates*, L. E. Warren, Bureau of Chemistry, Washington, D. C.; *Historian*, E. G. Eberle, 10 W. Chase St., Baltimore, Md.

"Henrik Ibsen—Pharmacist," by Lt. Commander L. H. Roddis.

"Superstition, Credulity and Skepticism: Three Bugbears with Which Pharmacy Has Always Had to Contend," by Charles Whitebread.

"C. Lewis Diehl," by John E. Kramer.

"Dr. John Tennent and Seneca Rattlesnake Root," by Ralph Bienfang.

"Binding Up a Wound," by Fred B. Kilmer.

"History of the Maryland Pharmaceutical Association," by E. F. Kelly.

"Fragment of Early Drug History in Ohio, the Shakers of Lebanon," by John Uri Lloyd.

"Development of the Mortar and Pestle," by John Thomas Lloyd.

"Gifts of the Gods to Primitive Man," by John Thomas Lloyd.

"The Early Days of Pharmacy in the West," by John T. Moore.

"Dover's Powder," Marie Lembeck and Edward Kremers.

"The First Pharmacopœia," by Edward Kremers.

"The Names by Which Paracelsus Has Been Known," by Edward Kremers.

"Paracelsus in Literature," by Edward Kremers.

"The Apothecary in Literature: A Contemporary of Lucca Landuci," by Edward Kremers.

"Rewriting the History of Percolation," by M. Wruble and Edward Kremers.

"History of the Iowa Pharmaceutical Association," by J. M. Lindly.

"Early Pharmacy and Pharmacists of Montana," by Charles E. Mollett.

"The History of Pharmacy in Kansas," by M. Noll.

"Historical Pharmacy in Minnesota," by Frederick J. Wulling.

"American Pharmacognosists of the Nineteenth Century," by Heber W. Youngken.

"Historical Pharmacy," by Louis Gershenfeld.

## PLANT SCIENCE SEMINAR.

**Officers:** *Chairman*, W. B. Day, 701 S. Wood St., Chicago, Ill.; *Vice-Chairman*, Frank H. Eby, Temple University, Philadelphia, Pa.; *Secretary-Treasurer*, O. P. M. Canis, Ozone Park, L. I., N. Y.

The Plant Science Seminar will be held in Madison, Wisconsin, August 21st to August 25th, with headquarters at the Chi Omega Sorority house at 115 Langdon St.

**Monday, August 21st, 9:00 A.M.**

Registration and Business Session.

Planning and Developing a Medicinal Plant Garden, Dr. B. V. Christensen.

History and Development of the University of Wisconsin Medicinal Plant Garden, Dr. W. O. Richtmann.

1:00 P.M. Trip to the Pharmaceutical Garden.

8:00 P.M. Colored Photographs of Medicinal Plants, Dr. M. E. Diemer.

**Tuesday, August 22nd, 9:00 A.M.**

Round-Table Discussion on Poisonous Plants, Dr. L. K. Darbaker.

1:00 P.M. Trip to the Forest Products Laboratory.

**Wednesday, August 23rd, 9:00 A.M.**

Session to Be Held at the Pharmacognosy Laboratory of the School of Pharmacy.

"Pharmacographia Americana," Dr. W. O. Richtmann.

"Phytochemistry of Digger Pine," Dr. A. H. Uhl.

1:00 P.M. Boat Trip on Lake Mendota.

8:00 P.M. Dr. Karl Link.

**Thursday, August 24th, 9:00 A.M.**

All-Day Field Collecting Trip, Blue Mounds, and the Valley of the Wisconsin River. Lunch at Spring Green.

8:00 P.M. Film Topics, Dr. L. K. Darbaker.

**Friday, August 25th, 9:00 A.M.**

Genus Mentha Symposium.

Display of Native and Cultivated Mints Grown at the Pharmaceutical Garden.

The Chemistry of the Mint Oils, Dr. Edward Kremers.

Our Native Menthas, Dr. F. J. Bacon.

1:00 P.M. Collecting Trip around the Madison Lakes and Pine Bluff.

5:00 P.M. Picnic Supper at the Home of Dr. Edward Kremers.

8:00 P.M. Campfire Talk.

## NATIONAL CONFERENCE ON PHARMACEUTICAL RESEARCH.

**Officers:** *Chairman*, E. N. Gathercoal, Chicago; *Vice-Chairman*, William J. Husa,

Gainesville, Fla.; *Secretary*, John C. Krantz, Jr., Baltimore; Fitzgerald Dunning, Baltimore. *Place of Meeting*, Madison, Wis. *Time*, 1933.

**First Session, 2:00 P.M.—Saturday, August 26th, Hotel Lorraine.**

1. Call to Order by Chairman.
2. Appointment of Nominating Committee.
3. Summary of Year's Activities and Outlook of Conference for the Future, by Chairman Gathercoal.
4. Reports of Officers.
   *a.* Report of Secretary.
   *b.* Report of Treasurer.
   *c.* Report of Executive Committee by Secretary.
5. Reports of Standing Committees.
   (1) Pharmaceutical Dispensing, W. J. Husa, Chairman.
   (2) Manufacturing Pharmacy, E. F. Cook, Chairman.
   (3) Medicinal Chemicals, George D. Beal Chairman.
   (4) Pharmacognosy, H. W. Youngken, Chairman.
6. Roll Call of Delegates.
7. Report of Special Committee on Fellowship Award, E. N. Gathercoal, Chairman.
   *a.* The announcement of the second award of the Fellowship of the National Conference on Pharmaceutical Research.
8. Adjournment for dinner. Arrangements will be made for an assembled dinner for the delegates.

An address pertinent to the work of the Conference will be delivered.

**Evening Session, 8:00 P.M.**

9. (5) Pharmacology and Bioassays, J. C. Munch, *Chairman*.
   (6) Bacteriology and Biologicals, A. R. Bliss, *Chairman*.
   (7) Physical Chemistry, C. B. Jordan, *Chairman*.
   (8) Educational Methods, A. B. Lemon, *Chairman*.
   (9) Pharmaceutical Economics, Ambrose Hunsberger, *Chairman*.
   (10) Historical Pharmacy, C. H. LaWall, *Chairman*.
10. Reports of other Special Committees.
   (1) Book on Research Achievements, John C. Krantz, Jr.
   (2) Census of Research, J. C. Munch, *Chairman*.
11. General Discussion of the Status of Pharmaceutical Research.
12. Election and Installation of Officers.
13. Adjournment.

JOHN C. KRANTZ, JR., *Secretary*.

## OFFICERS OF STATE PHARMACEUTICAL ASSOCIATIONS.

*References to some state associations will be supplemented in next issue.*

### ALABAMA.

Alabama Pharmaceutical Association elected the following officers at its meeting in Mobile: *President*, Fred Martin, Birmingham; *First Vice-President*, C. C. Thomas, Selma; *Second Vice-President*, N. G. Hubbard, Birmingham; *Secretary*, W. E. Bingham, Tuscaloosa; *Treasurer*, Hal E. Duncan, Birmingham; *Executive Committee*, Dora Megginson, E. M. Megginson and Samuel J. Watkins.

On recommendation of President Haynie, the Executive Committee was increased from three to five members and the state is to be grouped according to Congressional Districts.

### COLORADO.

The annual meeting of the Colorado Pharmaceutical Association was held in Colorado Springs, June 13th to 15th. The new officers are as follows: *President*, Sebastian Kletzky, Pueblo; *First Vice-President*, Wm. C. Alexander, Salida; *Second Vice-President*, Paul G. Stodghill, Denver; *Treasurer*, Julius F. Earnest, Denver; *Secretary*, Charles J. Clayton, Denver.

### CONNECTICUT.

Connecticut Pharmaceutical Association elected the following officers for the ensuing year: *President*, Edward J. Murphy, Manchester; *First Vice-President*, Wm. J. Coughlan, West Haven; *Second Vice-President*, Wm. J. Cody, Bridgeport; *Third Vice-President*, Joseph A. Murphy, Middletown; *Secretary-Treasurer*, P. J. Garvin, New Haven.

### DELAWARE.

Delaware Pharmaceutical Association held its annual meeting at same time and place with Maryland Pharmaceutical Association, at

Ocean City. The following officers were elected: *President*, Arthur H. Morris, Lewes; *First Vice-President*, Albert Bunin, Wilmington; *Second Vice-President*, Harry P. Jones, Smyrna; *Third Vice-President*, Edward J. Elliott, Bridgeville; *Secretary*, Albert Dougherty, Wilmington; *Treasurer*, Peter T. Bienkowski, Wilmington.

## FLORIDA.

Florida Pharmaceutical Association held its annual session at Tampa. Among the speakers of the Convention were P. A. Foote and B. V. Christensen.

The following officers were elected for the ensuing year: *President*, J. K. Clemmer, Miami; *First Vice-President*, Don Evans, Orlando; *Second Vice-President*, A. C. Hankins, Orlando; *Third Vice-President*, Victor Wray, Haines City.

## ILLINOIS.

The 54th annual meeting of the Illinois Pharmaceutical Association was held in Galesburg. Secretary H. C. Christensen of the National Association Boards of Pharmacy represented the A. PH. A. and spoke on the pharmacy exhibit at the Century of Progress.

The officers elected for the ensuing year are as follows: *President*, Arthur Van Hooser, Metropolis; *First Vice-President*, George V. Haering, Chicago; *Second Vice-President*, H. M. Anderson, Monmouth; *Third Vice-President*, L. Brown Hamilton, Galesburg; *Secretary*, W. B. Day, Chicago; *Treasurer*, George M. Bennett, Urbana.

## INDIANA PHARMACEUTICAL ASSOCIATION.

Indiana Pharmaceutical Association elected the following officers: *President*, Asa E. Smith, Logansport; *First Vice-President*, Harry G. May, Princeton; *Second Vice-President*, Ira V. Rothrock, Mt. Vernon; *Third Vice-President*, G. T. Revington, Monticello; *Secretary*, F. V. McCullough, New Albany; *Treasurer*, Harry J. Borst, Indianapolis.

Among the principal speakers of the meeting were Kiefer Mayer on "The Drug Institute," and Dr. J. H. Weinstein, president of the Indiana State Medical Association, discussed a report of the Committee on Costs of Medical Care. He was supported by Dean C. B. Jordan.

## KENTUCKY.

The 56th annual Convention of the Kentucky Pharmaceutical Association was held at Crab Orchard Springs, June 20th–23rd, and had the largest registered attendance in the history of the Association. The Association adopted a complete set of new by-laws.

The Kentucky Board of Pharmacy reported that it was carrying an injunction suit to the Court of Appeals asking for a decision or a ruling of the court as to whether or not general merchants may sell *all kinds* of patented or proprietary items. The contention of the Board being that poisons or strictly pharmaceutical items, whether patented or not, can be sold only by registered pharmacists. This case is now before the Kentucky Court of Appeals.

The following officers were elected for the coming year: *President*, George D. Duncan, Franklin; *Secretary*, J. W. Gayle, Frankfort; *Treasurer*, William J. Johnston, Mayfield; *Chairman of Executive Committee*, William H. Fischer, Louisville.

## MARYLAND.

Maryland Pharmaceutical Association at its meeting in Ocean City elected the following officers: *Honorary President*, Dr. D. M. R. Culbreth; *President*, L. V. Johnson, St. Michaels; *First Vice-President*, A. F. Ludwig, Baltimore; *Second Vice-President*, H. W. Matheney, Cumberland; *Third Vice-President*, M. Strasburger, Baltimore; *Secretary*, E. F. Kelly, 10 W. Chase St., Baltimore; *Treasurer*, Harry S. Harrison, Baltimore; *Editor*, R. L. Swain, Baltimore.

## MASSACHUSETTS.

Massachusetts State Pharmaceutical Association held its 52nd annual meeting at the New Ocean House, Swampscott, June 12th to 14th. Resolutions were adopted endorsing the Copeland Bill against counterfeiting drugs. More attention is to be given to the establishment of local associations and providing for their coöperation.

Appropriations were made for the attendance of the secretary at the Secretary's Conference in Madison. The following officers were elected for the ensuing year: *President* Martin E. Adamo, Boston; *First Vice-President*, Joseph A. Martin, Malden; *Second Vice-President*, T. Joseph McAuliffe, Lynn; *Treasurer*, Lyman W. Griffin, Boston; *Secretary*, Carl G. A. Harring, Newton.

## MICHIGAN.

Michigan Pharmaceutical Association elected the following officers for the ensuing year: *President*, Duncan Weaver, Fennville; *First Vice-President*, Paul Gibson, Ann Arbor; *Second Vice-President*, J. E. Mahar, Pontiac; *Treasurer*, Wm. H. Johnson, Kalamazoo; *Secretary*, R. A. Turrel, Croswell.

## MISSISSIPPI.

The Mississippi Pharmaceutical Association met in Jackson June 19th to 21st. The following officers were elected: *President*, G. C. Roberts, Greenwood; *First Vice-President*, Lew Wallace, Laurel; *Third Vice-President*, J. S. Puller, Starkville; *Secretary-Treasurer*, S. B. Key, Jackson.

It was decided to hold the 1934 meeting in Jackson.

## NEBRASKA.

Nebraska Pharmaceutical Association held its sessions at Lincoln, June 5th to 7th. Approval was given to the Drug Institute. The following officers were elected for the ensuing year: *President*, Fred J. Creutz, Wausa; *First Vice-President*, Guy Butler, Lincoln; *Second Vice-President*, Frank Cline, Auburn; *Third Vice-President*, R. W. Dunkle, Shelby; *Fourth Vice-President*, H. L. Bellamy, Cambridge; *Fifth Vice-President*, Fred V. Bors, Wilber; *Treasurer*, Orel Jones, Oconto; *Secretary*, J. G. McBride, Lincoln.

## NEW JERSEY.

The 63rd annual convention of New Jersey Pharmaceutical Association was held at Asbury Park, June 14th to 16th. Resolutions stressed the importance of U. S. P. and N. F. propaganda. Resolutions were adopted providing for a change in the pharmacy law to permit the Board of Pharmacy to examine graduates of approved colleges of pharmacy to qualify for theoretical examinations immediately after graduation and that the Board be given authority to regulate the type of practical experience to be required.

Another resolution provides that those named for the State Board of Pharmacy be qualified by education for the degree of Graduate in Pharmacy.

President Henry D. Kehr made a number of important recommendations which were adopted and which include organization of a Council of county delegates; appointment of an Emergency Relief Administration committee; prizes were provided for Pharmacy Week and also for students at the New Jersey College of Pharmacy.

The following officers were elected: *President*, Walter R. Woolley, Asbury Park; *First Vice-President*, Wm. H. Tegeler, Audubon; *Second Vice-President*, Wm. R. Richart, Elizabeth; *Secretary*, Prescott R. Loveland, Atlantic City; *Treasurer*, Charles J. McCloskey, Culver Lake.

## NEW MEXICO PHARMACEUTICAL ASSOCIATION.

The fifth annual convention of the New Mexico Pharmaceutical Association was held at Carlsbad. Taos was selected as the meeting place for 1934 and the following officers were elected: *President*, Roy E. Campbell, Fort Sumner; *First Vice-President*, S. J. Mollands, Taos; *Second Vice-President*, L. A. Rice, Albuquerque; *Secretary-Treasurer*, H. E. Henry, Albuquerque.

## NEW YORK PHARMACEUTICAL ASSOCIATION.

New York Pharmaceutical Association held its annual meeting at Stamford, June 20th–23rd. A total new membership of 1064 was enrolled, due largely to the efforts of Secretary Robert S. Lehman.

President Miller reviewed the work of the Association and many valuable papers and reports were received. Many important resolutions were adopted, among them one to support the Drug Institute when its code of procedure is known and endorsed by the Committee on Ethics.

The following officers were elected: *President*, John F. O'Brien, Rochester; *Vice-Presidents*, John Scavo, New York City; Henry J. Wildhack, Newark, N. Y.; Morris Brodkein, New York City; *Secretary*, Edward S. Dawson, Syracuse; *Treasurer*, Richard A. Austin, Cairo; *Members of the Executive Committee*, Fred C. Schaefer, Brooklyn; Curt P. Wimmer, New York City; Albert A. Muensch, Syracuse.

## NORTH CAROLINA.

North Carolina Pharmaceutical Association held its sessions in Charlotte, June 20th–22nd, and the attendance was larger than that of any preceding meeting. The Drug Institute re-

ceived consideration. Dues for proprietors were reduced to $10.00 and those of non-proprietors to $4.00. It was decided to cancel unpaid balances of delinquent members, provided such members paid their dues for the current year. Wrightsville Beach was selected for next year's convention and J. M. Hall was elected *Local Secretary*.

The following were installed as officers for 1933–1934: *President*, J. C. Hood, Kinston; *First Vice-President*, R. A. McDuffie, Greensboro; *Second Vice-President*, E. F. Rimmer, Charlotte; *Third Vice-President*, P. B. Bissette, Wilson; *Secretary-Treasurer*, J. G. Beard, Chapel Hill; *Member of the Executive Committee* for 3-year term, I. W. Rose, Chapel Hill.

## NORTH DAKOTA.

Dickinson was selected for the next place of meeting and the following officers were elected for the ensuing year: *President*, William Eckstrom, Stanley; *First Vice-President*, L. G. Beardsley, New Rockford; *Second Vice-President*, C. H. Saunders, Minot; *Secretary* W. F. Sudro, State College Station, Fargo; *Treasurer*, P. H. Costello, Cooperstown; *Local Secretary*, Phillip H. Boise, Dickinson. Place of Meeting, Dickinson.

## PENNSYLVANIA.

The Pennsylvania Pharmaceutical Association held its annual meeting at Bedford Springs Hotel, Bedford Springs, June 27th to 29th. The officers elected are as follows: *President*, Robert R. Gaw, Pittsburgh; *First Vice-President*, Frank P. Kelly, Carbondale; *Second Vice-President*, George W. Grier, Pittsburgh; *Secretary-Treasurer*, J. B. Pilchard, Harrisburg. *Executive Committee, Chairman*, C. Leonard O'Connell, Pittsburgh; Henry Brown, Scranton; John C. Walton, Philadelphia.

The 1934 meeting will be at Wernersville.

## SOUTH CAROLINA.

The South Carolina Pharmaceutical Association held its annual meeting June 14th and 15th, at Greenville. Officers were elected as follows: *President*, L. E. Bishop, Laurens; *First Vice-President*, V. F. Platt, Conway; *Second Vice-President*, George T. Kellers, Union; *Third Vice-President*, L. A. Melchers. Charleston; *Secretary and Treasurer*, J. M, Plaxco, Due West.

Charleston was chosen as the meeting place for 1934.

## SOUTH DAKOTA.

South Dakota Pharmaceutical Association elected the following officers for the ensuing year: *President*, Bliss Wilson, Letcher; *Vice-President*, George Lloyd, Spencer; *Vice-President as Chairman on Scientific and Practical Pharmacy*, L. A. Daniels, Aberdeen; *Vice-President as Chairman of Section on Education and Legislation*, N. B. Porter, Madison; *Secretary*, Roland Jones, Gettysburg; *Treasurer*, Frank S. Bockoven, Clark.

## VIRGINIA.

The officers of the Virginia Pharmaceutical Association elected for the years 1933–1934 are as follows: *President*, James M. Lea, Schoolfield; *Vice-Presidents*, Edw. P. Berlin, Berryville; Guy L. Miller, Charlottesville; Robt. G. Barr, Virginia Beach; Roy Crouch, Roanoke; H. S. Falconer, Newport News; W. G. Crockett, Richmond; *Secretary-Treasurer*, A. L. I. Winne, Richmond.

Hot Springs was selected for the next place of meeting, July 9th–11th.

## WISCONSIN.

Among the speakers at the 53rd annual convention at Green Lake were the following: G. A. Bender on "Ways to Build Up the Prescription Department;" H. C. Christensen on "The Pharmacy Exhibit at the World's Fair;" Edward Kremers on "Pharmacy and Its Status." President Oscar Rennebohm outlined Association activities and recommended *The Wisconsin Druggist* be continued.

The following officers were elected for the ensuing year: *President*, Otto H. Berndt, Manitowoc; *First Vice-President*, Edward J. Ireland, Madison; *Second Vice-President*, Paul Janke, Milwaukee; *Third Vice-President*, Dick Millbauer, Clintonville; *Secretary*, Ralph W. Clark, Madison; *Treasurer*, B. F. Leidel, Milwaukee.

## "MAXIMUM HOURS EXEMPTION" REQUIREMENT.

President Roosevelt in his recent message exempted from the "maximum hours" requirement *registered pharmacists* and other *professional* persons employed in *their profession*, and those employed in a management or executive capacity for more than $35.00 per week. Other exemptions are made, but do not directly apply to pharmacy.

### AMERICAN PHARMACEUTICAL MANUFACTURERS' ASSOCIATION.

The American Pharmaceutical Manufacturers' Association held its meeting at the Edgewater Beach Hotel, Chicago, June 21st. The officers elected for the ensuing year are as follows: *President*, Carl L. Angst, Indianapolis, Ind.; *Vice-Presidents*, E. G. Paisley, Philadelphia, Pa.; F. W. Misch, Lincoln, Nebr.; *Secretary*, C. W. Warner, Newark, N. J.; *Treasurer*, Frank A. Mallett, Des Moines, Iowa; *Members of the Board of Directors*, S. DeWitt Clough, North Chicago, Ill.; Elmer H. Hessler, New York City; John G. Searle, Chicago; Charles Wesley Dunn, Esq., was re-elected Counsel.

Among the subjects of discussion were the new Food and Drugs Bill and resolutions approved the amendment which prohibits false or misleading advertisements. Dr. Paul Nicholas Leech, secretary of the Council on Pharmacy and Chemistry of the American Medical Association, was one of the principal speakers; his subject was "Pharmaceutical Products of the Future."

The constructive purposes of the Drug Institute were approved.

### FEDERAL WHOLESALE DRUGGISTS' ASSOCIATION.

The meeting of the Federal Wholesale Druggists' Association was held June 27th–28th.

Resolutions were adopted that a code be filed on behalf of the Federal Wholesale Druggists' Association and its stockholders and customary members, etc., in view of the presentation of codes by so many other industries or subdivisions thereof at the present time. The Committee on Code is constituted as follows: *Chairman*, J. P. Jelenek, Minneapolis; F. T. Roosa, Cleveland; S. C. James, Buffalo; A. E. James, Baltimore; R. E. Lee Williamson, Baltimore; E. C. Brokmeyer, Washington.

### OFFICERS OF THE PROPRIETARY ASSOCIATION.

The following officers were elected at the recent meeting of the Proprietary Association: *President*, Frank A. Blair (reëlected); *Honorary Vice-President*, Dr. V. Mott Pierce; *First Vice-President*, Robert L. Lund; *Second Vice-President*, E. K. Hyde; *Third Vice-President*, J. H. Horne; *Secretary-Treasurer*, Charles P. Tyrell; *Members of the Executive Committee* for three years, John F. Murray, Ellery Mann and William Y. Preyer.

### PHARMACEUTICAL COLLEGES FOR WOMEN IN JAPAN.

Two pharmaceutical institutions for women, namely, the Showa Women's College of Pharmacy and the Women's Department of the Tokyo College of Pharmacy, have received official government recognition as to college standing on March 29th. About a year ago these colleges began preparations for such government recognition and the Education Department has favorably reported its findings.

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## LEGAL AND LEGISLATIVE.

### THE LEGAL RANGE OF THE BRITISH PHARMACOPŒIA.

The *Chemist and Druggist* of June 3rd discusses the legal range of the British Pharmacopœia, in part as follows:

"It is, of course, a fact that where there exist in commerce two standards for any article, that is to say (1) the standard with which the article must comply when required for medicinal use, and (2) the standard with which the article must comply when required for a commercial purpose apart from medicinal use, a chemist—or any one else, for that matter—is entitled to plead that unless the purchaser of the article makes it clear that he is buying the article for medicinal purposes, his demand is satisfied by the supply of an article which conforms to the recognized commercial standard. But, subject to this exception, we doubt, with all due respect to our learned contemporary, whether in practice there is any uncertainty as to the fact that when an article is required for medicinal use the courts will regard the supply of that which does not conform to the standard of the B. P. (when there is one) as an offense. Pharmacists, moreover, must expect, in virtue of their acknowledged position as suppliers of medicinal articles, that very slight evidence will raise a presumption that the article demanded is demanded for medicinal purposes, even where two standards exist. *Prima facie*, then, a

chemist who is asked for an article named in the Pharmacopœia by a name or synonym which appears in the Pharmacopœia ought to supply an article corresponding to the pharmacopœial standard; and, harsh though it may seem, there appears to be no reason to suppose that it would be any defense to him to say: 'The article I supplied would have corresponded with the Pharmacopœia but for the fact that a new edition has been published which fixes an altered standard.' Standards are altered—in theory at least—because in the opinion of the competent authority the altered standard is more desirable; and a pharmacist would surely be on poor ground in attempting to argue that the supply of an article corresponding to the presumably inferior standard of a former edition was an adequate compliance with the demand for an article named in the existing edition."

ONE RESULT OF ALTERED STANDARDS.

"It follows that, in theory, an inspector under the Food and Drugs Acts might within a few days after the publication of a new Pharmacopœia demand from a chemist an article the standard for which had been altered in that edition, and lay an information if he were supplied with an article which corresponded to the old but did not correspond to the new standard. Such an attempt would never be made, we assume, by any inspector with a proper view of his duties, nor should the local authorities sanction a prosecution in such circumstances. But, as chemists know to their cost, not all local authorities administer the Food and Drugs Acts with equal intelligence. There are still to be found districts in which the authority appears to value its inspectors in proportion to the number of convictions which can be secured by trapping blameless chemists and other traders into committing technical offenses. Probably this is a risk which can never be wholly eliminated."

## CONNECTICUT RESTRICTS USE OF WORD PHARMACY OR SYNONYM.

An Act concerning unauthorized use of the word "pharmacy" or synonym in Connecticut is quoted herewith:

"Be it enacted by the Senate and House of Representatives in General Assembly convened:

"Section 445*a* of the Cumulative Supplement of 1931 is amended to read as follows:

"Any person, firm or corporation owning, managing or conducting any store, shop or place of business not being a licensed pharmacy, exhibiting within or upon the outside of such store, shop or place of business, or including in any advertisement in a newspaper, book, magazine, circular or other printed matter, the words 'drug store,' 'pharmacy,' 'apothecary,' 'drug,' 'drugs,' 'medicine shop' or any combination of such terms or any other words indicating that such store, shop or place of business is a place where medicines are compounded, or exhibiting within or without such store, shop or place of business or in connection therewith any show bottle or globe of colored glass or filled with colored liquid, shall be fined not more than two hundred dollars or imprisoned not more than thirty days or both." H. B. 572. Public Health and Safety.

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# BOOK NOTICES AND REVIEWS.

*The Medicinal and Poisonous Plants of Southern Africa.* By JOHN MITCHELL WATT, M.B., Ch.B., Professor of Pharmacology in the University of the Witwatersrand, Johannesburg, and Maria Gerdina Breyer-Brandwijk, Phil. docta. (Utrecht), Apotheker (Utrecht). Formerly Junior Lecturer in Pharmacology and presently Research Worker in Phytochemistry in the Department of Pharmacology in the University of Witwatersrand, Johannesburg, 1933, pages xx + 314, 12 color plates and 20 illustrations. Price $8.25. Publishers, William Wood and Company, Baltimore, Maryland.

This book is an answer to the botanist's, pharmacognosist's and pharmacologist's prayer. A wealth of crude drugs have been coming from South Africa, and the number of these products has been increasing in recent years. The standard reference books have given only meager information, or none at all upon most of the new materials. In certain toxicological cases circumstantial evidence has suggested the use of some African poisonous plant but confirmation has been impossible because of the lack of authentic information.

The authors have arranged a system whereby specimens of medicines, charms or poisons are

obtained, together with their histories and uses. This represents an important step in collecting information on these widely scattered products. Some of the medicinal plants have been used in the preparation of secret remedies, without any clear information regarding the action of the product employed. It has been the aim of the authors to record "all the available information on the medicinal uses, chemical composition, pharmacological effects and the human and veterinary toxicology of the flora of Southern Africa."

The contents are arranged in 128 botanical families, well illustrated by color plates and illustrations. Pertinent bibliographic references are given throughout the text and accompanied by 28 general references to African medicinal plants. An index of botanical names is followed by an index of English and African names and by an index of native names. This will be very useful in identifying products discussed in various reports. An index of active principles greatly facilitates reference to the contents of the volume.

A very extensive and complete survey of the medicinal and poisonous plants of Southern Africa is presented which should prove of great value in further studies in medicine, pharmacy, phyto-chemistry and toxicology. The authors have kindly offered to assist correspondents in tracing the identity of plants, and it appears that much attention will be given to this proffered assistance. It is hoped that the information collected on African charms may be published to supplement the meager information we now have along this line.—JAMES C. MUNCH.

## PUBLICATIONS RECEIVED.

### PROCEEDINGS OF THE FIFTY-EIGHTH ANNUAL MEETING OF THE NATIONAL WHOLESALE DRUGGISTS' ASSOCIATION.

Proceedings of the 58th annual meeting of the National Wholesale Druggists' Association held at Green Brier Hotel, White Sulphur Springs, W. Va., September 1932.—The "Proceedings" follow the usual lines of reporting and contain much information that has value to all divisions of the drug-trade activities. The reports are of particular interest and among them those of the legislative and of the publicity Committees. The "Principles of Business Conduct" as passed at the 12th annual meeting of the Chamber of Commerce of the United States are included.

A valuable list is that of the publications issued by the Association, which includes bulletins which may be had from the National Wholesale Druggists' Association, 51 Maiden Lane, New York, N. Y. The mechanical part of the book is of the usual quality. A list of the officers is given and half-tones of the officers and Board of Control grace the pages.

*Whitla's Pharmacy Materia Medica and Therapeutics*, twelfth edition, revised by J. A. GUNN, Professor of Pharmacology in the University of Oxford, assisted by H. BERRY, head of the Department of Pharmacy, Birmingham, Central Technical College and J. CLIFFORD HOYLE, M.D., Medical Business Assistant and Administrator in Pharmacology, London Hospital, published by Wm. Wood & Co., Baltimore, price $4.25. The appearance of this book in its twelfth edition speaks to that extent of its usefulness. Materia Medica and Therapeutics are outstanding subjects in this work of about 700 pages. Previous editions of the book have been reviewed in the JOURNAL.

The International Pharmaceutical Federation has published a Report of the International Committee on Specialties. The committee is composed of Drs. H. Thoms,[1] Berlin; A. Rising, Stockholm; H. Baggesgaard Ramsusen, Copenhagen; W. Herissey, Paris; L. Van Italie, Leyden; Dr. E. Weis, Vienna, in coöperation with Dr. E. Host Madsen, Copenhagen and Dr. E. Schulek, Budapest.

General assay methods are described and defined. This is a most valuable report on various methods and assay processes.

The Wellcome Research Institution and the Wellcome Foundation, Ltd., have issued a handsomely prepared illustrated booklet of the exhibits at the Chicago Exposition. Represented in the exhibit are the Bureau of Scientific Research, the Entomological Field Laboratories, the Physiological Research Laboratories, the Chemical Research Laboratories, the Historical Medical Museum and the Museum of Medical Science.

The Wellcome Research Institution and the Affiliated Research Laboratories and Museums were founded by Sir Henry Wellcome. Aside from being a directory of the exhibit the booklet contains much useful information.

[1] Deceased.